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Contents

Cardiovascular Disorders	7
Stable Angina Pectoris	7
Congestive Heart Failure	11
Hypertension	15
Pulmonary Disorders	21
Allergic Rhinitis and Conjunctivitis	21
Asthma	24
Chronic Obstructive Pulmonary Disease	25
Smoking Cessation	25
Infectious Diseases	27
Pneumonia	27
Sinusitis	29
Pharyngitis	31
Management of the HIV-Infected Patient	31
Diverticulitis	33
Urinary Tract Infection	35
Herpes Simplex Virus Infections	37
Herpes Zoster	39
Syphilis	41
Tuberculosis	41
Tetanus Prophylaxis	43
Infectious Conjunctivitis	43
Gastrointestinal Disorders	45
Gastroesophageal Reflux Disease	45
Peptic Ulcer Disease	47
Constipation	49
Acute Diarrhea	52
Chronic Diarrhea	54
Neurologic Disorders	57
Headache	57
Vertigo	60
Epilepsy	63
Dementia and Alzheimer's Disease	66
Endocrinologic, Renal, and Orthopedic Disorders	69
Hyperlipidemia	69
Type I Diabetes Mellitus	72
Type II Diabetes Mellitus	76
Low Back Pain and Osteoarthritis	81
Dermatologic Disorders	87
Acne Vulgaris	87
Dermatitis and Verruca Vulgaris	89
Dermatitis	89

Verruca Vulgaris (Common Skin Warts)	90
Common Skin Diseases	91
Alopecia Areata	91
Scabies	91
Acne Rosacea	91
Seborrheic Dermatitis	92
Drug Eruptions	92
Groin Rashes	93
Nail Infections	93
Tinea Versicolor	94
Dermatophytosis	95
Pityriasis Rosea	95
Bacterial Infections of the Skin	96
Furuncles and Carbuncles	96
Superficial Folliculitis	96
Impetigo	96
Cellulitis	97
Psoriasis	97
Pruritus Ani	98
Gynecologic Disorders	101
Management of the Abnormal Pap Smear	101
Contraception	103
Oral Contraceptives	103
Injectable Depot Medroxyprogesterone Acetate	105
Contraceptive Implants	105
Intrauterine Devices	106
Postcoital Contraception	106
Endometriosis	107
Premenstrual Syndrome	108
Amenorrhea	109
Breast Disorders	113
Nipple Discharge	113
Breast Pain	113
Fibrocystic Complex	114
Menopause	114
Osteoporosis	116
Abnormal Uterine Bleeding	118
Pelvic Inflammatory Disease	121
Sexually Transmitted Diseases	123
Gonorrhea	123
Chlamydia Trachomatis	124
Vaginal Infections	124
Bacterial Vaginosis	124
Candida Vulvovaginitis	125
Trichomonas Vaginitis	126
Pubic Infections	127
Human Papilloma Virus	127
Molluscum Contagiosum	127
Pediculosis Pubis	128
Pubic Scabies	128

Urologic Disorders	129
Benign Prostatic Hyperplasia	129
Prostatitis and Prostatodynia	131
Acute Epididymorchitis	133
Psychiatric Disorders	135
Depression	135
Anxiety Disorders	138
Generalized Anxiety Disorder	138
Panic Disorder	138
Insomnia	141
Index	144
References	148

Cardiovascular Disorders

Stable Angina Pectoris

Angina pectoris is characterized by chest pain or by choking, suffocation, squeezing, pressure, or burning in the chest or adjacent areas.

Angina pectoris is considered to be stable when anginal episodes have occurred with a consistent frequency for a month or more. Symptoms are usually brought on by exertion or emotional stress; however, 30% of patients experience some episodes at rest.

I. Pathophysiology. Angina is caused by severe atherosclerotic narrowing of one or more coronary arteries. The result is an inadequate oxygen supply to meet myocardial demands during exercise or emotional stress.

II. Prognosis

- A. Patients with left main coronary artery disease and patients with three-vessel disease and poor left ventricular function (ejection fraction $<50\%$) have the poorest prognosis.
- B. One-, two-, or three-vessel disease and good left ventricular function (ejection fraction $>50\%$) has a relatively better prognosis, such that the incidence of myocardial infarction and death is similar with medical therapy or bypass surgery.
- C. Stable angina associated with normal coronary arteries (syndrome X and microvascular angina) has a good prognosis.

III. Clinical Evaluation

- A. The history should evaluate the severity and frequency of anginal symptoms.
 1. The effect of exercise and stress should be documented, and the occurrence of episodes at rest, and relief of symptoms by nitroglycerin should be sought.
 2. In the elderly, angina may present as episodes of dyspnea on exertion.
- B. **Physical examination, electrocardiography, and chest radiography** are useful for excluding concomitant conditions, including valvular disease, heart failure, and peripheral vascular disease.
- C. **Laboratory testing** should exclude anemia, valvular heart disease, and thyrotoxicosis, diabetes, and hypercholesterolemia.

IV. Laboratory Detection of Coronary Artery Disease

- A. **Exercise ECG stress testing** can identify high-risk patients.
 1. Good left ventricular function or the ability to exercise more than 6 minutes on the treadmill using a Bruce protocol are indicative of relatively low risk.
 2. The exercise ECG test has a sensitivity of only 70%, and the specificity of the test is only 75%. The exercise test is of greatest clinical benefit for patients with an intermediate probability of coronary disease.
 3. The exercise test is accurate for assessing the severity of known cardiac disease.
 4. Digoxin, antiarrhythmics, LBBB, WPW, and LVH will complicate the interpretation of the exercise test. These patients require either a stress echo or a stress nuclear perfusion study. These tests are used when the exercise test is non-diagnostic or when the clinical impression and the exercise test differ.
- B. **Echocardiography or radionuclide angiography** to evaluate resting left ventricular function can identify high-risk patients.

8 Stable Angina Pectoris

- C. **Single photon emission computer tomography (SPECT) technetium sestamibi imaging** is useful for localizing regions of ischemia. Technetium based agents, particularly technetium sestamibi have replaced thallium as the radionuclide of choice for stress perfusion studies.
- D. **Stress echocardiography.** If coronary artery disease is present, exercise will cause an ischemic area of the heart to stop thickening normally. These stress induced wall motion changes can be detected using stress echocardiography. Stress echo has the advantages of reduced cost, no exposure to radioactivity, and added information about valvular, LV and pericardial disease.
- E. In patients who cannot exercise, a Persantine SPECT sestamibi is as accurate as an exercise test. Persantine causes generalized coronary vasodilation. Normal coronaries experience a greater increase in coronary flow than diseased coronaries. Persantine echo is not as useful as the Persantine nuclear perfusion study. However, dobutamine infusion in conjunction with serial echocardiography provides an accurate non-exercise, assessment of coronary artery disease.
- F. **Coronary angiography** is not indicated in low risk patients. It is indicated in patients with diminished left ventricular function who either cannot exercise for 6 minutes or who have a large reversible defect on thallium stress testing.

V. Management of Stable Angina Pectoris

- A. Smoking cessation should be recommended because smoking increases risk.
- B. Conditions known to aggravate angina, such as anemia, thyrotoxicosis, or arrhythmias, should be treated. Hypertension, diabetes, and hypercholesterolemia should be treated.
- C. **Estrogen replacement therapy** is prescribed for post-menopausal women.
- D. **Coronary artery bypass surgery** is appropriate initial therapy for patients with significant left main coronary artery disease or for patients with triple-vessel disease and poor left ventricular function.
- E. **Aspirin** reduces cardiovascular morbidity and mortality in men and women; one 81-325-mg tablet daily.
- F. **Nitrates**
 - 1. Nitrates dilate coronary stenosis and increase collateral blood flow to ischemic areas.
 - 2. Nitrates should not be used continuously because of the development of tolerance. A daily nitrate-free interval, is recommended.
 - 3. **Immediate-Release Nitroglycerine**
 - a. Nitroglycerine, sublingually or in spray form, is the only agent that is effective for rapid relief of an established angina attack.
 - b. Patients should carry nitroglycerin tablets or spray at all times and use it as needed.
 - c. Nitroglycerine SL (Nitrostat), 0.3-1.5 mg SL q5min prn pain [0.15, 0.3, 0.4, 0.6 mg].
 - d. Nitroglycerine oral spray (Nitrolingual) 1-2 sprays prn pain.
 - 4. **Nitroglycerin Patches:** Tolerance may be avoided by removing it for 8 hours per 24 hour period. A minimum of 15 mg of nitroglycerin per 24-hr period is necessary for effect. Nitroglycerine patch (Transderm-Nitro) 0.6-0.8 mg/h applied for 16 hours each day [0.4, 0.6, 0.8 mg/h patches].
 - 5. **Indications.** First-line monotherapy with long-acting nitrates is effective in most patients with stable angina. However, treatment increases angina-free walking distance for only 8-12 hours during the day. Patients who have early morning or nocturnal symptoms should use a transdermal nitroglycerine product. The patch should be left on overnight and removed at 2 PM every day for 8 hours, then reapplied.

6. Isosorbide Dinitrate

- a. Isosorbide dinitrate immediate-release, 30 mg tid-qid.
- b. Isosorbide dinitrate slow-release, (Dilatrate-SR, Isordil Tembids) are taken bid-tid.
- c. Isosorbide dinitrate (Isordil, Titrados) 10-60 mg PO tid-qid [5, 10, 20, 30, 40 mg]; sustained release, 40-80 mg PO q8-12h [40 mg].

7. Isosorbide Mononitrate

- a. Isosorbide mononitrate is an active metabolite of isosorbide dinitrate.
- b. **Isosorbide mononitrate immediate release (ISMO, Monoket)** is given as 10 to 20 mg bid in the morning and again 7 hours later [10, 20 mg].
- c. **Isosorbide mononitrate extended-release (Imdur):** Start with 30 mg and increase the dose to 120 mg once daily [30, 60, 120 mg].

8. Adverse Effects

- a. Nitrates are well tolerated. The most common adverse effect is headache (30-60%).
- b. Symptomatic postural hypotension may sometimes occur. Syncope may rarely occur.

G. Beta-adrenergic Blockers

1. Beta blockers are the most effective of the antianginal drugs for reducing ambulatory ischemia. They reduce myocardial oxygen demand by reducing heart rate, contractility, and systolic blood pressure during exercise.
2. **Indications.** Beta blockers are highly effective as monotherapy for angina and are the drug of choice for postinfarction angina and in patients with concomitant hypertension or supraventricular tachycardia.
3. Beta blockers may precipitate heart failure because of their negative inotropic effects.
4. All beta blockers are equally effective at increasing angina-free walking distance.
5. The cardioselective agents, atenolol (Tenormin) and metoprolol (Lopressor), are as effective as the non-cardioselective agents propranolol (Inderal) and nadolol (Corgard). Cardioselective agents are preferred in patients with diabetes or pulmonary disease.

6. Non-cardioselective Beta-Blockers

- a. **Propranolol immediate-release (Inderal),** 80-160 mg bid-qid [10, 20, 40, 60, 80, 90 mg].
- b. **Propranolol sustained-release (Inderal LA),** 60-160-mg qd [60, 80, 120, 160 mg].
- c. **Nadolol (Corgard),** 40-80 mg qd [20, 40, 80, 120, 160 mg].
- d. **Timolol (Blocadren)** 5-10 mg PO tid-qid [5, 10, 20 mg].
- e. **Carvedilol (Coreg)** 6.25-50 mg bid [6.25, 12.5, 25 mg].

7. Cardioselective Beta-Blockers

- a. **Metoprolol (Lopressor),** 25-100 mg bid [25, 50, 100 mg].
- b. **Atenolol (Tenormin),** 50-200-mg qd [25, 50, 100 mg].
- c. **Acebutolol (Sectral)** 200-600 mg bid [200, 400 mg].
- d. **Betaxolol (Kerlone)** 10-20 mg qd [10, 20 mg].
- e. **Bisoprolol (Zebeta)** 5-20 mg qd [5, 10 mg].

8. Adverse Effects

- a. Beta blockers are usually well tolerated. Symptomatic bradycardia, hypotension, fatigue, heart failure, dyspnea, cold extremities, and bronchospasm may occur. Impotence, constipation, and vivid dreams may occasionally occur.
- b. **Contraindications to Beta-Blockers**
 - (1) Raynaud's phenomenon, reactive airway disease, or resting leg or foot pain caused by peripheral vascular disease.
 - (2) Beta blockers (including cardioselective agents) can cause severe bronchospasm in patients with reactive airway

disease.

9. Calcium Channel Blockers

- a. Calcium channel blockers are effective as first-line monotherapy for angina in patients who have contraindications to beta-blocker therapy.
- b. Verapamil and diltiazem are effective in episodic supraventricular tachycardia; however, dihydropyridines (amlodipine, felodipine, nifedipine, nicardipine) should be avoided.
- c. All calcium channel blockers cause varying degrees of vasodilation and thus reduce myocardial oxygen demand and increase coronary blood flow.
- d. Diltiazem and verapamil reduce exercise-induced heart rate increases.
- e. Dihydropyridines cause significant vasodilation, and they have a minimal effect on SA and AV nodal conduction.
- f. All calcium channel blockers can depress left ventricular function.
- g. **Dosages**
 - (1) Nifedipine XL (Procardia XL), 30-120 mg qd [30, 60, 90 mg].
 - (2) Amlodipine (Norvasc) 2.5-10 mg qd [2.5, 5, 10 mg].
 - (3) Felodipine (Plendil) 5-10 mg qd-bid [5, 10 mg]
 - (4) Diltiazem SR (Cardizem SR) 60-120 mg bid [60, 90, 120 mg].
 - (5) Diltiazem CD (Cardizem CD) 120-300 mg qd [120, 180, 240, 300 mg]
 - (6) Verapamil SR (Calan SR, Isoptin SR), 120-240 mg qd [120, 180, 240 mg].
- h. **Adverse Effects**
 - (1) Calcium channel blockers are well tolerated. Leg edema occurs more often with dihydropyridines than with diltiazem or verapamil.
 - (2) Constipation is often a problem with verapamil.
 - (3) Diltiazem and verapamil are contraindicated in second degree or higher atrioventricular block, and should be used with caution if given in combination with beta-blockers or other agents that block the AV node.
 - (4) Calcium channel blockers should be used with caution in heart failure.

H. Combination Therapy for Stable Angina

1. When symptoms cannot be adequately controlled with monotherapy, combination therapy is initiated.
2. Nitrates plus beta blockers are well tolerated, and they increase exercise duration and reduce angina frequency.
3. Nitrates combined with diltiazem, verapamil, or second-generation dihydropyridines are well tolerated.
4. Triple therapy is generally not recommended.

I. Management of Refractory Angina

1. Bepridil (Vascor)

- a. Bepridil, a calcium channel blocker, is used for patients who are not candidates for revascularization, who have not responded to other drugs. 200 to 400 mg qd [200, 300, 400 mg].
- b. Bepridil prolongs the QT interval and can cause ventricular arrhythmias (Torsade de pointes), especially when hypokalemia or hypomagnesemia is present. The QT-interval, serum potassium, and serum magnesium levels are monitored.

2. **Coronary artery bypass surgery or balloon angioplasty** should be considered in patients who do not respond to medical treatment.

References: See page 148.

Congestive Heart Failure

I. Clinical Evaluation of Heart Failure

- A. All patients who complain of paroxysmal nocturnal dyspnea, orthopnea, or new-onset dyspnea on exertion should undergo evaluation for heart failure unless history and physical examination clearly indicate a noncardiac cause (obstructive pulmonary disease, pneumonia).
- B. Chest pain may indicate that ischemia is the cause of heart failure; however, ischemia can also occur without chest pain.
- C. Edema, heart murmur, prior viral illness, hypertension, myocardial infarction, alcohol or drug use, thyroid disease, or lung disease should be sought. The degree of physical impairment should be determined.
- D. **Precipitating Cause.** The most common precipitating cause is lack of compliance with dietary and medical regimens. Atrial arrhythmias such as fibrillation and flutter sometimes exacerbate CHF without the patient being aware of any change in heart rhythm. Nonsteroidal anti-inflammatory agents, alcohol, beta blockers (including eyedrops), calcium blockers, most antiarrhythmic drugs, and some anti-neoplastic drugs can precipitate or exacerbate CHF.

II. Physical Exam Findings

- A. Elevated jugular venous pressure and a third heart sound are the most specific findings, and they are virtually diagnostic in patients with compatible symptoms.
- B. Pulmonary rales or peripheral edema are relatively nonspecific findings.
- C. Abdominal jugular reflex is a better clinical indicator of heart failure than pulmonary rales. Press on the patient's abdomen and observe jugular veins for distension.

Conditions That Mimic or Provoke Heart Failure

Coronary artery disease and myocardial infarction
 Hypertension
 Aortic or mitral valve disease
 Cardiomyopathies: Hypertrophic, idiopathic dilated, postpartum, genetic, toxic, nutritional, metabolic
 Myocarditis: Infectious, toxic, immune
 Pericardial constriction

Tachyarrhythmias or bradyarrhythmias
 Pulmonary embolism
 Pulmonary disease
 Congenital abnormalities
 High output states: Anemia, hyperthyroidism
 A-V fistulas, Paget's disease, fibrous dysplasia, multiple myeloma
 Renal failure, nephrotic syndrome

III. Laboratory Evaluation of Heart Failure

- A. Echocardiogram, CXR, EKG
- B. Electrolytes, BUN, creatinine, magnesium, liver function tests
- C. CBC, urinalysis
- D. Thyroid stimulating hormone (if atrial fibrillation, evidence of thyroid disease, or age >65 yrs)

Clinical Evaluation of Laboratory Studies

Test	Finding	Possible Diagnosis
Electrocardiogram	Acute ST-T wave changes	Myocardial ischemia
	Atrial fibrillation, other tachyarrhythmia	Thyroid disease or heart failure due to rapid ventricular rate
	Bradyarrhythmias	Heart failure due to low heart rate
	Previous myocardial infarction (Q waves)	Heart failure due to reduced left ventricular performance.
	Low voltage	Pericardial effusion

12 Congestive Heart Failure

Complete blood count	Anemia	Heart failure due decreased oxygen-carrying capacity
Urinalysis	Proteinuria	Nephrotic syndrome
Serum creatinine	Elevated	Volume overload due to renal failure
Thyroid-stimulating hormone	Abnormal	Heart failure due to hypothyroidism or hyperthyroidism

E. Chest Roentgenogram. Cardiomegaly, pleural effusions, or pulmonary vascular redistribution may be seen.

F. Electrocardiogram often reveals evidence of old myocardial infarction, hypertrophy, and/or conduction system delays.

G. Echocardiography or Radiographic Ventriculography

1. Left ventricular function evaluation is a critical step in the evaluation and management of patients with suspected or apparent heart failure.
2. Echocardiography is used to differentiate between dilated cardiomyopathy, left ventricular diastolic dysfunction, valvular heart disease, or a noncardiac etiology.
3. Most patients with heart failure are found to have ejection fractions of less than 40%.
4. **MUGA Scanning.** In a relatively small proportion of patients, usually those who are markedly obese or have emphysema, a echocardiogram does not adequately visualize the ventricles. The multiple gated acquisition (MUGA) scan measures ventricular function. For this test to be accurate, the patient must have a regular heart rhythm; therefore, in patients with atrial fibrillation, a first-pass study should be ordered rather than a MUGA scan.

IV. Management of Congestive Heart Failure

A. Angiotensin Converting Enzyme Inhibitors

1. ACE inhibitors should be prescribed for all patients with left ventricular systolic dysfunction unless contraindicated (serum potassium level greater than 5.5 mEq/L, or symptomatic hypotension).
2. Diuretics should be added if symptoms persist despite treatment with ACE inhibitors.
3. ACE-inhibitors have an enhanced first-dose response that may occur in patients with hyponatremia or dehydration; very low initial doses should be prescribed.
4. **Side effects of ACE-inhibitors** include postural hypotension, renal insufficiency, and hyperkalemia. Less serious, but also common, is development of a chronic dry cough. At times, the cough may be lessened by decreasing the dose, but often the drug must be discontinued. If the patient is intolerant of ACE inhibitors, the combination of hydralazine and isosorbide is most commonly used.

Drug Treatment of Heart Failure

Drug	Initial Dose	Target Dose	Max Dose	Adverse Reactions
Loop Diuretics Furosemide (Lasix)	10-40 mg qd	40-80 mg qd-bid	240 mg bid [20, 40, 80 mg]	Postural hypotension, hypokalemia, hyperglycemia, hyperuricemia, rash; rare severe reaction includes pancreatitis, bone marrow suppression and anaphylaxis
Torsemide (Demadex)	5-10 mg qd	20-40 mg qd	100 mg bid	Same as furosemide
Bumetanide (Bumex)	0.5 mg qd	1-2 mg qd	2 mg bid	Same as furosemide
ACE Inhibitors Enalapril (Vasotec)	2.5 mg bid	10 mg bid	20 mg bid	Hypotension, hyperkalemia, renal insufficiency, cough, skin rash, angioedema, neutropenia
Lisinopril (Prinivil, Zestril)	5 mg qd	20 mg qd	40 mg qd	Same as enalapril
Quinapril (Accupril)	5 mg bid	20 mg bid	20 mg bid	Same as enalapril
Captopril (Capoten)	6.25-12.5 mg tid	50 mg tid	100 mg tid	Same as above
Digoxin	0.125 mg qd	As needed	As needed	Cardiotoxicity, confusion, nausea, dizziness, tachycardia, lupus-like syndrome

B. Diuretics

1. Diuretics are useful for reducing symptoms of volume overload, including orthopnea and paroxysmal nocturnal dyspnea. Diuretics should be started immediately when patients present with symptoms or signs of volume overload.
2. Diuretics reduce intravascular volume and reduce preload.
3. Adequate diuretic dosage is indicated by neck veins that are flat and by the absence of perforated edema.
4. Loop diuretics (furosemide, bumetanide, torsemide) are diuretics of first choice. Severe congestive symptoms require a twice daily regimen because of fluid accumulation during the day. The second daily dose should be given by mid-afternoon to avoid nocturnal diuresis.
5. Torsemide has greater oral absorption and a longer duration of action than furosemide or bumetanide. Bumetanide has the shortest duration of action, requiring bid dosing.
6. **Adverse Effects.** Orthostatic hypotension or abnormalities of fluid and

14 Congestive Heart Failure

electrolyte balance (hypokalemia, hypomagnesemia) may occur, which predispose to arrhythmias.

7. Serum magnesium and potassium levels should be monitored and supplemented when necessary.

C. Inotropic Therapy

1. Digoxin

- a. Digoxin increases the force of ventricular contraction in patients with left ventricular systolic dysfunction. Physical functioning and symptoms improved with digoxin.
- b. Digoxin should be initiated along with ACE inhibitors and diuretics in patients with severe heart failure.
- c. Patients with mild to moderate heart failure will often become asymptomatic with optimal doses of ACE inhibitors and diuretics, and these patients do not require digoxin. Digoxin should be added to the regimen if symptoms persist despite optimal doses of ACE inhibitors and diuretics.
- d. Digoxin level should be kept between 1.0 and 2.0 ng.
- e. Digoxin is ineffective and contraindicated in patients without cardiomegaly who have preserved systolic function, reduced ventricular compliance, and diastolic dysfunction.

D. Beta Blockers

1. Low-dose beta blockers may produce long-term improvements in heart failure. In patients with catecholamine excess, beta blockers may be very beneficial. However, beta blockers may also cause acute deterioration.
2. **Carvedilol (Coreg)** should be considered in all heart failure patients if they are limited by symptoms or are deteriorating on conventional therapy. Initiate at low dosage and increase dose slowly; 6.25-50 mg bid.
3. **Metoprolol (Lopressor)** may be given to patients with compensated CHF at 6.25 mg PO bid for 1 week followed by a doubling of the dose every week as tolerated until 50 mg bid or symptoms appear.

V. Intravenous Inotropic Agents

- A. Dobutamine (Dobutrex) 2.5-10 $\mu\text{g/kg/min}$, max of 14 $\mu\text{g/kg/min}$ (500 mg in 250 mL D5W, 2 $\mu\text{g/mL}$) titrate to CO >4, CI >2
- B. Milrinone (Primacor) 50 mcg/kg IV over 10 min, followed by 0.375-0.75 (average 0.5) mcg/kg/min IV infusion (40 mg in 200 mLs NS (QS), conc=0.2 mg/mL).

VI. Revascularization

- A. Coronary artery disease is the most common cause of heart failure, and some patients may benefit from revascularization.
- B. In patients without a history of myocardial infarction, angina, or recurrent pulmonary edema, physiologic tests for ischemia (sestamibi scanning) or coronary angiography should be completed.

VII. Non-Pharmacologic Measures

- A. Patients should be informed about symptoms of worsening heart failure, and they should keep a record of their daily weights. If worsening of symptoms or a weight gain of 3-5 lb or more occurs within one week, the patient should and take an extra dose of diuretic.
- B. **Regular exercise** is encouraged.
- C. **Dietary Therapy**
 1. Dietary sodium should be restricted to 2 g per day.
 2. Total fluid intake of 1.5-2 L/day should be maintained, and excessive fluid intake should be avoided. Fluid restriction is not advisable unless hyponatremia is present.
 3. Alcohol should be discouraged, and patients should consume no more than one drink per day.

References: See page 148.

Hypertension

Hypertension is defined as a systolic blood pressure (SBP) greater than 140 mm Hg and/or a diastolic blood pressure (DBP) above 90 mm Hg. There is elevated risk of morbidity and mortality at all levels of hypertension.

I. Clinical Evaluation

- A. Evaluation of hypertension includes an assessment of missed doses of maintenance antihypertensive therapy, use of nonsteroidal anti-inflammatory drugs, decongestants, diet medications, cocaine, or amphetamines.
- B. The medical history should seek the presence of coronary heart disease (chest pain), hyperlipidemia, diabetes, smoking, or prostatic hypertrophy because these disorders may influence the choice of antihypertensive.
- C. **Physical Examination of the Hypertensive Patient**
 1. Blood pressure should be measured with the patient seated for at least 5 minutes. An appropriate size cuff should be used.
 2. Retinal hemorrhages, exudates, arteriovenous crossing defects, carotid bruits, left ventricular enlargement, coarctation of the aorta, aortic aneurysm, and absence of a peripheral pulse in an extremity are sought.
- D. **Initial Diagnostic Evaluation of Hypertension**
 1. **12 lead electrocardiography** may document evidence of ischemic heart disease, rhythm and conduction disturbances, or left ventricular hypertrophy.
 2. **Urine analysis.** Dipstick testing for glucose, protein, hemoglobin.
 3. Complete blood count, glucose, potassium, calcium, creatinine, BUN, uric acid, and fasting lipid panel.
 4. Selected patients may require plasma renin activity, plasma catecholamines, 24 hour urine for metanephrines, or renal function testing (glomerular filtration rate and blood flow).

Classification of Blood Pressure

Category	Systolic	Diastolic	Recommended Follow-up
Normal	<130 mm Hg	<85 mm Hg	Recheck in 2 years
High normal	130-139 mm Hg	85-89 mm Hg	Recheck in 1 year
Stage I hypertension	140-159 mm Hg	90-99 mm Hg	Reevaluate within 2 months
Stage II hypertension	160-179 mm Hg	100-109 mm Hg	Evaluate and treat within 1 month
Stage III hypertension	180-209 mm Hg	110-119 mm Hg	Evaluate and treat within 1 week
Stage IV hypertension	>210 mm Hg	>120 mm Hg	Evaluate and treat immediately

II. Findings Suggesting Secondary Hypertension

- A. **Primary Aldosteronism.** Initial serum potassium <3.5 mEq/L while not taking medication.
- B. **Aortic Coarctation.** Femoral pulse delayed later than radial pulse or posterior systolic bruits below ribs.
- C. **Pheochromocytoma.** Orthostatic hypotension, tachycardia, tremor, pallor.

16 Hypertension

- D. **Renovascular Stenosis.** Paraumbilical abdominal bruits.
- E. **Polycystic Kidneys.** Flank or abdominal mass.
- F. **Pyelonephritis.** Persistent urinary tract infections, costovertebral angle tenderness.
- G. **Renal Parenchymal Disease.** Increased serum creatinine ≥ 1.5 mg/dL, proteinuria.

Screening Tests for Secondary Hypertension

Renovascular Hypertension	Captopril Test: Plasma renin level before and 1 hr after captopril 25 mg PO. A greater than 150% increase in renin is positive Captopril Renography: renal scan before and after 25 mg PO Intravenous pyelography MRI angiography Arteriography (DSA)
Hyperaldosteronism	Serum Potassium 24 hr urine potassium Plasma renin activity CT scan of adrenals
Pheochromocytoma	24 hr urine metanephrine Plasma catecholamine level CT scan Nuclear MIBG scan
Cushing's Syndrome	Plasma ACTH Dexamethasone suppression test
Hyperparathyroidism	Serum calcium Serum parathyroid hormone

III. Non-drug Treatment of Hypertension

A. Lifestyle Modification

1. Lifestyle modification is step 1 therapy for most patients with mild hypertension.
2. Dietary changes that reduce weight and decrease alcohol and sodium consumption are recommended. Aerobic exercise and relaxation therapy may also reduce BP.
3. Appropriate dietary sodium intake ranges from 1.5-2.5 g of sodium, or 4-6 g of salt. A 2-g sodium diet requires the omission of foods naturally high in sodium, limitation of salt used in seasoning, and limitation of prepackaged fast-foods.
4. Alcohol intake should be limited to no more than 1 oz of ethanol a day.
5. Lifestyle modification is tried for a minimum of 3-6 months in most patients before initiating medications. In individuals with low cardiovascular risk, the threshold for drug therapy is raised to 160/100 mm Hg and lifestyle modification used for at least one year.

IV. Pharmacologic Management of Hypertension

- A. Beta blockers and diuretics are the preferred medications for hypertension because a reduction in morbidity and mortality has been demonstrated. Angiotensin-converting enzyme (ACE) inhibitors, calcium entry blockers, and alpha blockers are alternative medications, although these agents have not been shown to reduce morbidity and mortality.
- B. Demographic profile and comorbid risk factors may help in selecting the type of medication.
- C. Treatment should begin with a low dose of medication from one class. If a low dose of one type of medication is not effective after 1-3 months,

medication from a different category may be substituted for the first, or a low dose of a second medication from a different class may be added, or the dose of the first medication may be increased.

D. Selection of Antihypertensive Drug

1. Thiazide diuretics in low doses (25 mg) are recommended for Africans, the elderly, smokers, and persons with a normal ECG.
2. Beta-blockers are recommended for whites, nonsmokers, younger patients, and those with CHD.
3. ACE inhibitors are useful for whites, younger patients, those with a total cholesterol greater than 240 mg/dL, and diabetics.
4. Calcium entry blockers may be used for the elderly, Africans, and those with hypercholesterolemia.
5. Alpha-1 blockers are useful for men with prostatic hyperplasia.
6. ACE inhibitors, calcium entry blockers, and alpha-1 antagonists cause the least interference with sexual function.

V. Classification of Antihypertensive Drugs

A. Thiazide Diuretics

1. Thiazide diuretics have consistently been shown to lower BP. They have similar efficacy, except that metolazone and indapamide are more effective in moderate renal insufficiency.
2. **African hypertensives** respond less well to treatment with beta-blockers than whites; therefore, diuretics are a better option.
3. **Elderly persons** with hypertension have a much lower adrenergic contribution to hypertension. Thus, diuretics have an advantage.
4. **Effects of Thiazides on Lipids.** Thiazide diuretics increase LDL cholesterol in the short term; however, there is little evidence that these changes are maintained for more than one year.
5. **Effects of Thiazides on Glucose.** Diuretics and beta blockers may provoke glucose intolerance, and they are contraindicated in diabetics.
6. **Effects of Thiazides on Potassium**
 - a. Thiazide diuretics induce a decrease in serum potassium with chronic therapy.
 - b. Hypokalemia can usually be avoided by administering no more than 50 mg per day. If the thiazide dose is increased to >25 mg, a potassium sparing diuretic combination should be used (Dyazide).

7. Diuretics

- a. **Hydrochlorothiazide (HCTZ, HydroDiuril)**, initial dose 12.5 mg qd; 25-100 mg qd-bid [25, 50, 100 mg].
- b. **Chlorothiazide (Diuril)** 250-500 mg qd-bid [250, 500 mg].
- c. **Chlorthalidone (Hygroton)** 15-100 mg qd [15, 25, 50, 100 mg].
- d. **Indapamide (Lozol)** 1.25-5 mg qd [1.25, 2.5 mg].

8. Thiazide/Potassium Sparing Diuretic Combinations

- a. **Maxzide** (triamterene/hydrochlorothiazide: 37.5/25 mg, 75/50 mg) 1-2 tabs qd.
- b. **Moduretic** (amiloride 5 mg/hydrochlorothiazide 50 mg) 1-2 tabs/d in 1-2 doses.
- c. **Dyazide** (triamterene/hydrochlorothiazide: 37.5/25 mg, 50/25 mg) 1-2 caps qd-bid.

B. Beta-Adrenergic Blockers

1. All beta adrenergic blockers are equally effective in the treatment of hypertension. Cardioselective beta blockers become less selective as the dosage is increased, but they may offer advantages in patients with diabetes or chronic lung disease.
2. Africans are more responsive to diuretics and calcium entry blockers compared to beta blockers and ACE inhibitors. Beta blockers are more effective in whites compared to Africans.
3. Beta-blockers have a cardioprotective effect and reduce mortality in persons who have had a myocardial infarction. These drugs are the

18 Hypertension

agents of choice in patients with coronary heart disease.

4. Effects on Lipids, Glucose, and Potassium

- Beta blockers are associated with HDL cholesterol decreases, and LDL cholesterol increases in short term studies.
- They should be avoided in patients with a marked elevation in LDL cholesterol.
- Beta blockers should be avoided in insulin requiring diabetes because they mask symptoms of hypoglycemia.

5. The lipophilic beta blockers (propranolol, acebutolol, timolol, metoprolol, pindolol) do not cause more CNS symptoms than the hydrophilic beta blockers (atenolol, nadolol), contrary to prior belief.

6. Cardioselective Beta-Blockers

- Metoprolol (Lopressor)** 50-100 mg bid, max 450 mg/d [50, 100 mg]. Metoprolol XL (Toprol XL) 50-200 mg qd [50, 100, 200 mg tab ER]
- Atenolol (Tenormin)** initial dose 50 mg qd, then 50-100 mg qd, max 200 mg/d [25, 50, 100 mg].

7. Non-Cardioselective Beta-Blockers

- Propranolol LA (Inderal LA)**, 80-160 mg qd [60, 80, 120, 160 mg] or propranolol (Inderal) 40-160 mg bid; max 320 mg/day [10, 20, 40, 60, 80, 90 mg].
- Timolol (Blocadren)** 5-10 mg bid, max 60 mg/d [5, 10, 20 mg].
- Nadolol (Corgard)** 40-80 mg qd, max 320 mg/d [20, 40, 80, 120, 160 mg].
- Pindolol (Visken)** 5-20 mg qd, max 60 mg/d [5, 10 mg].
- Carteolol (Cartrol)** 2.5-10 mg qd [2.5, 5 mg].

C. Angiotensin-Converting Enzyme (ACE) Inhibitors

- ACE inhibitors have similar effectiveness; however, they differ in half-life.
- Africans** respond less well to ACE inhibitors.
- Diabetes**
 - ACE inhibitors are the agents of choice for diabetics because they slow the progression of renal failure.
 - Hyperkalemia is a risk when using ACE inhibitors in diabetics.
- Heart Failure.** ACE inhibitors are beneficial in reversing heart failure in patients with hypertension.
- Adverse Effects**

- Chronic cough is the major adverse effect. 11.5% of patients on captopril and 24.7% of patients on enalapril complain of cough. Longer acting ACE inhibitors may be more likely to induce cough.
- Reversible renal insufficiency may occur, and a rise in creatinine of up to 0.5 mg/dL is tolerable. ACE inhibitors should at creatinine >2.5 mg/dL.

6. ACE Inhibitors

- Ramipril (Altace)** 2.5-10 mg qd, max 20 mg/day [1.25, 2.5, 5, 10 mg].
- Quinapril (Accupril)** 20-80 mg qd-bid; max 80 mg/day [5, 10, 20, 40 mg].
- Lisinopril (Zestril, Prinivil)** 10-40 mg qd; max 40 mg/d [2.5, 5, 10, 20, 40 mg].
- Benazepril (Lotensin)** 10-40 mg qd, max 80 mg/day [5, 10, 20, 40 mg].
- Fosinopril (Monopril)** 10-40 mg qd, max 80 mg/day [10, 20 mg].
- Enalapril (Vasotec)** 5-40 mg qd or bid, max 40 mg/day [2.5, 5, 10, 20 mg].
- Moexipril (Univasc)** 7.5 mg qd; max 30 mg/day [7.5 mg].
- Captopril (Capoten)** 25-150 mg bid-tid; max 450 mg/day [12.5, 25, 50, 100 mg].

D. Calcium Entry Blockers

1. Calcium entry blockers have no adverse effects on lipids.
2. They should be used with caution in heart failure because of negative inotropic effects.
3. Calcium entry blockers do not have the cardioprotective benefit following myocardial infarction (that is associated with beta-blockers).
4. These agents work equally well in Africans and whites.
5. **Diltiazem SR (Cardizem SR)** 60-120 mg bid; max 360 mg/d [60, 90, 120 mg] or **Cardizem CD** 180-360 mg qd [120, 180, 240, 300 mg].
6. **Nifedipine XL (Procardia-XL, Adalat-CC)** 30-90 mg qd, max 120 mg/d [30, 60, 90 mg].
7. **Verapamil SR (Calan SR, Covera-HS)** 120-240 mg qd, max 480 mg/d [120, 180, 240 mg].
8. **Amlodipine (Norvasc)** 2.5-10 mg qd [2.5, 5, 10 mg tabs].
9. **Felodipine (Plendil)** 5-10 mg qd, max 10 mg/d [2.5, 5, 10 mg].
10. **Isradipine (DynaCirc)** 2.5-5 mg bid, max 20 mg/d [2.5, 5 mg].
11. **Nicardipine SR (Cardene-SR)** 30-60 mg bid [30, 45, 60 mg].

E. Alpha-1 Receptor Blockers

1. The alpha-1 blockers offer no advantage over other medications, except that they reduce symptoms in prostatic hyperplasia.
2. **Doxazosin (Cardura)** 1-16 mg qhs, max 16 mg/d [1, 2, 4, 8 mg].
3. **Terazosin (Hytrin)** 1-20 mg qhs; max 20 mg qd [1, 2, 5, 10 mg].
4. **Prazosin (Minipress)** 1-10 bid-tid [1, 2, 5 mg]; short-acting agent.

F. Combination Agents

1. **Lotrel (amlodipine/benazepril)** one cap qd [2.5/10, 5/10, 5/20 mg].
2. **Lotensin (benazepril/HCTZ)** one tab qd [5/6.25, 10/12.5 mg].
3. **Hyzaar (losartan/HCTZ)** one tab qd-bid [50/12.5].
4. **Vaseretic (enalapril/HCTZ)** 1-2 tab PO qd [10/25 mg]

References: See page 148.

Pulmonary Disorders

Allergic Rhinitis and Conjunctivitis

Allergic rhinitis characterized by sneezing, rhinorrhea, nasal congestion, and pruritus of the nose, eyes or throat. Peak incidences are in childhood and adolescence.

I. Clinical Evaluation of Allergic Rhinitis and Conjunctivitis

- A. **Signs and Symptoms:** Allergic rhinitis is characterized by repetitive sneezing, rhinorrhea, nasal congestion, pruritic eyes, ears, nose, or throat. Chronic cough (postnasal drip) and sinus headaches may occur. Symptoms may be perennial and/or seasonal in onset.
- B. **Aggravating Factors** may include grass, dust, leaves, or animals.
- C. Historical data include a family history of allergy, a personal history of atopy, age at onset of symptoms, medication use, and history of nasal trauma.
- D. Allergic rhinitis is frequently divided into two types, seasonal and perennial, based on the time of symptom onset and duration.
- E. Seasonal allergic rhinitis symptoms include tearing and conjunctival discharge and chronic nasal obstruction. Perennial symptoms occur throughout the year and may be related to dust mites or animal dander.
- F. **Physical Examination**
 1. Thoroughly examine eyes, ears, nose, throat, neck, and lungs.
 2. **Nasal Mucosa** will appear pale and boggy, with serous secretions, and edematous turbinates.
 3. **Ocular examination** reveals injection of the bulbar conjunctiva, accompanied by a clear discharge.
 4. Patients may exhibit darkening under their eyes (allergic shiners) or a nasal crease under nose from rubbing.

Differential Diagnosis

Diagnosis	Etiology	Symptoms	Pattern of occurrence
Allergic rhinitis	IgE	Congestion Rhinorrhea Sneezing Pruritus	Perennial or seasonal
Nonallergic rhinitis eosinophilia syndrome	Unknown	Rhinorrhea Sneezing Pruritus Anosmia	Perennial
Polyps	Unknown	Congestion Anosmia Postnasal drip, often unilateral	Perennial
Vasomotor rhinitis	Autonomic dysfunction	Congestion Rhinorrhea Anosmia Postnasal drip	Perennial

22 Allergic Rhinitis and Conjunctivitis

Infection	Viral upper respiratory infection Bacterial sinusitis	Purulent rhinorrhea Fever	Perennial
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- G. Atopic diseases, such as eczema or asthma, are common in patients with allergic rhinitis. A deviated septum, foreign body or tumor suggest alternate diagnoses. Blood pressure should be recorded, because the medications used to treat allergic rhinitis may cause hypertension.
- H. Skin testing, the gold standard of diagnosis, is indicated when immunotherapy is a consideration.

II. Treatment of Allergic Rhinitis and Conjunctivitis

A. Environmental Modification

1. Avoidance of allergens that precipitate symptoms is the first step in management.
2. Symptoms during times of high humidity implicates dust mites or mold spores as causative agents. Killing of dust mites with acaricides is effective.
3. Animals should be kept outdoors, and windows should be kept closed and air conditioners used. Dust-proof covers are placed over pillows and mattress, and frequent dusting with a damp cloth and cleaning of floors is helpful.
4. High-efficiency particulate air (HEPA) cleaners or electronic cleaners installed in the central furnace are effective.

B. **Pharmacologic management** begins with an antihistamine. If congestion is present, an oral decongestant is added. If antihistamines and/or decongestants do not effectively relieve symptoms, intranasal corticosteroids or intranasal cromolyn is prescribed.

C. Antihistamines

1. Antihistamines are effective in controlling sneezing, pruritus and rhinorrhea, they do not alleviate congestion.
2. The first-generation H antihistamines are associated with a higher incidence of sedative and anticholinergic effects.
3. The second-generation H antihistamines, such as astemizole (Hismanal) and loratadine (Claritin), do not cause the sedation or anticholinergic effects of first-generation agents. Caution should be exercised when prescribing a second-generation antihistamine for patients with serious hepatic impairment or for patients who are concurrently taking drugs that undergo significant hepatic metabolism such as ketoconazole, itraconazole, clarithromycin, erythromycin, cimetidine, and disulfiram (Antabuse). The recommended dose should not be exceeded when prescribing astemizole because potentially fatal cardiac arrhythmias may occur.
4. **Loratadine (Claritin)** one tab qd [10 mg]. Not associated with Torsades de Pointes arrhythmias. Loratadine (Claritin) is not affected by food.
5. **Fexofenadine (Allegra)** 60 mg bid; metabolite of terfenadine; concurrent administration with erythromycin and ketoconazole is safe.
6. **Cetirizine (Zyrtec)** 5-10 mg PO qd [5, 10 mg]; mild bronchodilatory effect; does not prolong the QT interval.
7. **Astemizole (Hismanal)** 10 mg qd [10 mg]. Onset of effect may be delayed by 2-3 days. Food should not be ingested 1 hour before or 2 hours after; associated with weight gain; may prolong QT interval.

D. Decongestants

1. Intranasal and systemic decongestants relieve nasal congestion. Caution is advised when using decongestants in patients with cardio-

vascular disease, hypertension, diabetes, glaucoma, hepatic or renal impairment, or prostatic hypertrophy.

2. Sustained-release formulations, such as pseudoephedrine, are available in combination with second-generation antihistamines. Second-generation fixed-dose combinations are associated with a higher incidence of insomnia, nervousness or irritability.
3. **Pseudoephedrine (Sudafed)** 60 mg tid [tabs: 30, 60 mg], or sustained release caps: 120 mg bid, or topical spray 0.25-0.5% 1-2 sprays q4h.
4. Phenylpropanolamine (Entex) 25 mg q4-6h [25, 50 mg] or Entex SR 75 mg bid [75 mg].
5. Oxymetazoline (Afrin) (0.5%) 2-3 drops or sprays in each nostril bid-tid.
6. Use of intranasal decongestants for more than 3 to 4 days can cause rebound vasodilatation and nasal obstruction (rhinitis medicamentosa).

E. Topical Nasal Corticosteroids

1. Intranasal corticosteroids are the most effective agents for allergic rhinitis. They decrease edema and inflammation. The different intranasal corticosteroids are equally efficacious in relieving symptoms.
2. They are used twice daily, although once-daily administration is adequate after symptoms have been controlled. Improvement of symptoms may take up to a week and daily use is necessary. Aqueous solutions are more soothing to nasal tissues and cause less irritation and epistaxis.
3. **Beclomethasone (Beconase AQ)** AQ with 84 mcg/inhalation 2 sprays qd, or AQ or MDI in 42 mcg/inhalation 2 sprays bid. 6 to 12 years: 1 inhalation per nostril 3 times daily; <6 years: not recommended
4. **Flunisolide (Nasalide AQ)** 2 sprays bid. 6 to 14 years: 1 spray per nostril 3 times daily; <6 years: not recommended
5. **Triamcinolone acetonide (Nasacort AQ or MDI)** 2 sprays bid. <12 years: not recommended
6. **Budesonide (Rhinacort MDI)** 2 puffs in each nostril bid. 6 to 12 years: 2 sprays per nostril 2 times daily or 4 sprays per nostril once daily; <6 years: not recommended
7. **Fluticasone (Flonase AQ)** 2 sprays per nostril bid. ≥12 years: 1 spray per nostril daily. <12 years: not recommended
8. Corticosteroids may occasionally cause nasal irritation, burning, or bloody nasal discharge. If nosebleeds occur, the steroid spray is discontinued for a week, a saline spray is substituted. Petroleum jelly is applied with a cotton swab. An aqueous preparation should be used if nosebleeds occur.

F. Mast Cell Stabilizers

1. Delayed onset of action, short duration of activity, and inferior efficacy compared to corticosteroids are disadvantages.
2. Cromolyn (Nasal crom) 1 puff in each nostril tid-qid, max 6 times/day.
3. Cromoglycate (Rynacrom) 1 spray in each nostril qid.

G. Saline nose sprays such as Ocean Nasal Mist and NaSal can be helpful in moisturizing nasal tissues and dislodging mucus.

H. Ophthalmic Therapy

1. Ophthalmic decongestant preparations are useful in patients who have conjunctivitis. Naphazoline 0.1% (Naphcon), phenylephrine (Neo-Synephrine) and oxymetazoline (OcuClear, Visine LR) may be used alone or in combination with ophthalmic antihistamines such as antazoline (Vasocon-A) or pheniramine maleate (Naph-con-A).
2. Cromolyn ophthalmic (Crolom), 1-2 drops in each eye q4-6h, is a highly effective mast cell stabilizer.
3. Levocabastine (Livostin) is an ocular antihistamine that acts quickly, offering relief within a few minutes. One drop qid treats all the symptoms of conjunctivitis.
4. Ketorolac (Acular) is an ocular NSAID; 1 drop qid is effective for seasonal allergic conjunctivitis; use is limited to one week.

24 Asthma

5. Lodoxamide (Alomide), an ocular mast cell stabilizer, is used qid to treat seasonal allergic conjunctivitis; use should be limited to 3 months or less.
6. Adverse effects of levocabastine, ketorolac and lodoxamide include transient burning and stinging of the eyes. Concurrent use is not recommended in patients who wear soft contact lenses.

I. **Immunotherapy** is indicated for patients with allergic rhinitis do not obtain symptomatic relief with environmental modification or pharmacotherapy.

References: See page 148.

Asthma

Labs: CBC, ABG. CXR, pulmonary function tests. Peak flow rate.

General Measures: Environmental control (avoidance of dust, animals, use of mattress covers); use of air filters and air conditioning.

Beta Agonists:

- Albuterol (Ventolin) aerosol 2 puffs q4-6h prn, or powder 200 mcg/capsule inhaled qid prn, or 2-4 mg PO tid-qid [2, 4 mg]; or albuterol Repetab 4-8 mg PO bid prn [4 mg].
- Albuterol (Ventolin) or Metaproterenol nebulized, 0.2-0.5 mL (2.5 mg) in 3 mL saline q20min initially, then q2-8h prn.
- Metaproterenol (Alupent, Metaprel) 1-2 puffs qid-tid prn, or 10-20 mg PO q6-8h [10, 20 mg tablets].
- Pirbuterol (Maxair) 1-2 puffs q4-6h prn.
- Bitolterol (Tornalate) 2-3 puffs q1-3min initially, then 2-3 puffs q4-8h prn.
- Fenoterol (Berotec) 3 puffs initially, then 2 puffs bid-qid prn.
- Salmeterol (Serevent) 2 puffs bid; not for prn use or acute asthma.

Combination Agent:

- Combivent (albuterol/ipratropium) 2-4 puffs qid.

Corticosteroids:

- Beclomethasone (Beclovent) 2-6 puffs tid-qid, with spacer 5min after bronchodilator, followed by gargling with water.
- Triamcinolone (Azmecort) 1-4 puffs tid-qid.
- Fluticasone (Flovent) 2-4 puffs bid; not for acute bronchospasm.
- Flunisolide (AeroBid) 2-4 puffs bid.
- Methylprednisolone (Solu-Medrol); 30-60 mg PO qd [2, 4, 8, 16, 24, 32 mg]. Medrol dose pack, tapering dose starting at 24 mg and tapering over 7 days.
- Prednisone (Meticorten) 5-60 mg PO qAM [Deltasone 5, 10, 20, 50 mg].

Anti-Leukotrienes

- Used for prophylaxis and chronic treatment of asthma; it should not be used for bronchospasm in acute asthma attacks. These agents are only modestly effective for mild-to-moderate asthma. Inhaled steroids remain the treatment of choice for asthma prophylaxis.
- Zafirlukast (Accolate) 20 mg PO bid on an empty stomach [20 mg]; a leukotriene receptor antagonist. Coadministration with Warfarin significantly prolongs the prothrombin time.
- Zileuton (Zyflo) 600 mg PO qid [600 mg]; a leukotriene synthetase inhibitor; this agent inhibits the metabolism of Warfarin and theophylline.

Cromolyn:

- Cromolyn sodium (Intal) 2 puffs qid or powder 20 mg/capsule inhaled qid or 2 mL nebulized qid (1% sln, 20 mg); use for prevention and prophylactically for exercise-induced asthma 30 minutes before exposure or activity.
- Nedocromil sodium (Tilade) 2 puffs qid [16.2 gms]; use for prevention.

Theophylline (Second Line Therapy):

- Theophylline sustained release (Theo-Dur, Elixophyllin, Uniphyll) 100-400 mg bid-tid (3 mg/kg q8h or 9 mg/kg/d as single dose or in 2-3 doses) [100, 200,

300, 450 mg].

References: See page 148.

Chronic Obstructive Pulmonary Disease

Labs: ABG, CBC. CXR, pulmonary function tests, peak flow rate; ECG, PPD.

Treatment:

Beta Agonists, Acute Treatment:

- Nebulized Albuterol (Ventolin) or Metaproterenol (Alupent) 0.2-0.5 mL (2.5 mg) in 3 mL of saline q20min initially then q2-8h.
- Albuterol (Ventolin) or Metaproterenol (Alupent) 2-8 puffs, with spacer; then 2 puffs q4-6h.

Corticosteroids:

- Triamcinolone (Azmecort) 2-4 puffs qid with spacer, 5 min after bronchodilator, followed by gargling with water.
- Beclomethasone (Beclivent) 2-6 puffs qid.
- Flunisolide (AeroBid) 2-4 puffs bid.
- Fluticasone (Flovent) 2 puffs bid.
- Methylprednisolone (Solu-Medrol) 32-64 mg PO qd [8, 16, 24, 32 mg] or Medrol dose pack starting at 24 mg/d and tapering over 7 days.
- Prednisone 40-60 mg PO qd, taper gradually to minimum dose [10, 20, 50 mg].

Theophylline:

- Theophylline long acting (Theo-Dur) PO loading dose of 4.5 mg/kg, then maintenance of 100-400 mg bid-tid (3 mg/kg q8h) [100, 200, 300, 450 mg].

Acute Exacerbations of Bronchitis

Treat 7-10 days.

Trimethoprim/Sulfamethoxazole (Septra DS) 160/800 mg bid.

Amoxicillin/clavulanate (Augmentin) 500 mg tid or 875 mg bid [250, 500, 875 mg]; gastrointestinal side effects (diarrhea) are common. The 875 mg regimen has fewer GI side effects.

Cefuroxime axetil (Ceftin), 250-500 mg bid; good activity against primary pathogens.

Cefixime (Suprax), 400 mg qd; lacks Staphylococcus aureus coverage.

Loracarbef (Lorabid), 400 mg bid; moderate activity against beta-lactamase-producing strains of H influenzae.

Doxycycline (Vibramycin), 100 mg bid; not affected by beta-lactamase producers, S pneumoniae resistance in 10%-20%.

Azithromycin (Zithromax), 500 mg on day 1, then 250 mg qd after meals x 4 days.

Clarithromycin (Biaxin), 250-500 mg bid; moderate activity against H influenzae.

References: See page 148.

Smoking Cessation

I. Clinical Evaluation of Nicotine Withdrawal

A. Symptoms: Anxiety, craving, insomnia, depression, difficulty concentrating; hunger, impatience, insomnia, irritability, and restlessness.

B. If the patient has failed to quit smoking because of these withdrawal symptoms, then pharmacotherapy is indicated.

II. Pharmacologic Aids

A. Nicotine nasal spray (Nicotrol NS) achieves higher serum levels than nicotine patches; 1 spray in each nostril, q1-2 times/h; max 5 doses/h or 40 doses/d. The full dose is given for 8 weeks, then tapered over the next

26 Smoking Cessation

4 weeks. Nasal irritation may occur. [10 mg/mL, 10 mL (200 actuations)]

B. Nicotine Transdermal

1. **Side Effects:** Pruritus, erythema, and burning at application site.
2. **Nicotine Toxicity:** Smoking while using patch or using multiple patches may cause toxicity manifest by nausea, dizziness, hypotension, convulsions, angina, and respiratory failure.
3. **Dosages**
 - a. Transderm Nicotine (Nicoderm, Habitrol) initial dose 21 mg/day for up to 6 weeks, then 14 mg/day for 2 weeks, then 7 mg/d for 2 weeks; max 8 weeks [7, 14, 21 mg/patch].
 - b. Transderm Nicotine (ProStep) initial dose 22 mg/day for 4-8 weeks then 11 mg/day x 2-4 weeks; max 12 weeks [11, 22 mg/patch].

C. Nicotine Polacrilex (Nicorette):

1. Must be chewed slowly over 30-45 minutes whenever urge to smoke occurs. 10-12 pieces/d; max 30 pieces per day [2.4 mg, 96 pieces/box].
2. May be appropriate for those smokers who have a strong desire for an oral nicotine method; has a bitter taste; longer durations of therapy (more than 3 months) appear to be helpful.

III. Smoking Cessation Behavioral Therapy

- A. **Set a Stop Date:** Share the date with supportive family and friends, and write the date in a written contract.
- B. **Keep a smoking journal** of daily smoking habits for several days including time of day and the circumstances or situations associated with smoking.
- C. **Identify Alternative Behaviors:** Chew sugarless gum to keep mouth busy; keep hands busy with other activities when experiencing the urge to smoke.
- D. **Establish a Reward System:** Put all the money that previously would have been spent on cigarettes in a jar, and decide on a reward on which to spend the money. Mark smoke-free days on a calendar. Increase contact with friends who have quit.
- E. **Behavioral therapy** in addition to nicotine therapy increases quit rates by a factor of 1.6-1.8. Behavioral therapy may be especially indicated in smokers with a history of psychiatric, alcohol and drug problems.

IV. Failed Attempts with Transdermal Nicotine

- A. If dependent smokers fail to quit with transdermal nicotine therapy, determine the causes of the relapse and screen for psychiatric, alcohol and drug problems. Determine whether the patient experience relapse because of withdrawal (intense craving) or some nonwithdrawal event (receipt of bad news).
- B. If the relapse was due to withdrawal, consider adding nicotine nasal spray or gum to transdermal nicotine or consider using higher doses of transdermal nicotine (two patches, a 21-mg patch and a 14-mg patch).
- C. If the relapse was due to a non-withdrawal event, then group behavioral therapy in addition to transdermal nicotine therapy is recommended.

References: See page 148.

Infectious Diseases

Pneumonia

Pneumonia remains a common cause of death. *Streptococcus pneumoniae* is the most common etiologic agent identified, however, many bacteria, viruses, and fungi can cause pneumonia.

I. Clinical Evaluation

- A. Pneumonia typically manifest with cough productive of yellow-green, even blood-streaked sputum; dyspnea, pleuritic chest pain, fevers (often spiking to 104° F), chills, and shaking rigors are common.
- B. The chest examination reveals consolidation, including an area of dullness to percussion, and increased breath sounds (bronchial type).
- C. The organisms that cause typical pneumonias are usually the bacterial pathogens *Streptococcus pneumoniae* and *Hemophilus influenzae*.
- D. **Chest Radiography** is useful for differentiating bronchitis.

1. If no infiltrate is seen on x-ray, pneumonia is virtually excluded, even for dehydrated, elderly patients. Infiltrates may not be detected in 10-15% of AIDS patients with *P. carinii* pneumonia.

E. Gram's Stain and Culture

1. Squamous epithelial cells in large numbers suggests that the specimen is contaminated with upper respiratory secretions; the specimen should have <10 squamous epithelial cells per low power field. WBC's indicate a lower respiratory source of sputum.
2. Sputum culture reports should always be interpreted in light of the Gram stain results.

- F. **Blood Cultures** can occasionally provide additional diagnostic information in hospitalized patients, particularly in HIV infected patients.

G. Specialized Tests:

1. Acid-fast stain and culture for tuberculosis.
2. Specific tests for *Legionella pneumophila*, fungi, viruses
3. **Serologic tests:** Complement fixation (M pneumoniae), ELISA (IgM and IgA) for M pneumoniae.
4. Indirect fluorescent antibody test (L pneumophila); micro-immunofluorescence (*Chlamydia pneumoniae*).

- H. **Atypical Pneumonia** is defined as pneumonia for which none of the usual bacterial causes are evident. Systemic complaints are more prominent than respiratory complaints, especially gastrointestinal symptoms. The patient does not appear acutely ill, there is an insidious onset rather than abrupt onset, and a non-productive cough. Hilar or segmental lower lobe infiltrates are seen on chest films.

I. Pathogens Causing Community Acquired Pneumonia in Adults:

1. *Streptococcus pneumoniae* (most common cause), *H. influenzae* (especially if underlying lung disease), *Mycoplasma pneumoniae*, oral anaerobes (aspiration pneumonia), and, less commonly, *Staphylococcus aureus* and gram negative bacilli or viruses.
2. *Moraxella catarrhalis* may cause respiratory infection. *Legionella* species and *Chlamydia pneumoniae* (TWAR) are linked to a significant number of cases.
3. *P. carinii* pneumonia and other opportunistic pathogens are often associated with HIV infection. Tuberculosis has been seen increasingly (especially in AIDS).

Conditions Predisposing to Specific Pathogens

Condition	Common Pathogens
Alcoholism	Oral anaerobes, gram-negative bacilli, S pneumoniae
Nursing home residency	S pneumoniae, gram-negative bacilli, H influenzae
COPD	H influenzae, S pneumoniae, Moraxella catarrhalis
Influenza	Influenza virus, S pneumoniae, Staph aureus
Poor dental hygiene	Oral anaerobes
Travel	Endemic mycoses
Exposure to birds	Chlamydia psittaci
HIV infection	Pneumocystis carinii, S pneumoniae, H influenzae, M tuberculosis

II. Outpatient Management of Pneumonia

A. Treatment of Atypical Pneumonia

1. Erythromycin, 500 mg qid; not effective for pneumonia caused by H influenzae.
2. Clarithromycin (Biaxin), 500 mg bid.
3. Azithromycin (Zithromax), 500 mg x 1 dose, then 250 mg qd x 4 days [250, 500 mg].
4. Doxycycline (Vibramycin, Vibra-Tabs), 100 mg bid; most strains of S pneumoniae and H influenzae are susceptible to doxycycline.

B. Treatment of Typical Pneumonia

1. Community-acquired pneumonia is more likely to be caused by H influenzae or S pneumoniae and less likely to be caused by M pneumoniae.
2. Cefuroxime axetil (Ceftin), 500 mg bid.
3. Cefpodoxime (Vantin), 200 mg q12h
4. Loracarbef (Lorabid), 400 mg bid.
5. Amoxicillin/clavulanate (Augmentin) 500 mg tid or 850 mg bid, plus erythromycin or other macrolide.
6. **Allergy to Penicillin:** Trimethoprim-sulfamethoxazole (TMP-SMZ) one DS tab bid or doxycycline 100 mg bid.

References: See page 148.

Sinusitis

Sinusitis affects 12% of adults and is believed to complicate 0.5% of viral upper respiratory infections. Symptoms that last less than 1 month are indicative of acute sinusitis, while symptoms of longer duration reflect chronic sinusitis.

I. Pathophysiology

- A. Factors that predispose to sinus infection include anatomic abnormalities, viral URIs, allergies, overuse of topical decongestants, asthma, and immune deficiencies.
- B. **Acute sinusitis** is associated with the same bacteria as otitis media. Streptococcus pneumoniae, Hemophilus influenzae, and Moraxella catarrhalis are the most commonly encountered pathogens. 35% of H influenzae and 75% of M catarrhalis strains produce beta-lactamases.
- C. **Chronic sinusitis** is associated with Staphylococcus aureus and anaerobes. Frequently recovered anaerobes include the gram-positive cocci (eg, Peptostreptococcus and Peptococcus species) and Bacteroides species.

II. Clinical Evaluation

- A. If symptoms have lasted for less than 7 to 10 days and the patient is recovering, a self-limited viral URI is the most likely cause. However, worsening symptoms or symptoms that persist for more than 7 days are more likely to be caused by sinusitis.
- B. Symptoms of acute sinusitis include facial pain or tenderness, nasal congestion, purulent nasal and postnasal discharge, headache, maxillary tooth pain, malodorous breath, fever, and, occasionally, eye swelling. Pain or pressure in the cheeks and deep nasal recesses is frequent.
- C. High fever and signs of acute toxicity are unusual except in the most severe cases.
- D. Purulent drainage in the patient's nose or throat may sometime be apparent. A middle ear effusion may be present if the eustachian tube is obstructed by swelling.
- E. The nasal cavity can be examined with a nasal speculum or an otoscope. The nasal mucosa is erythematous and swollen. The presence of mucopus in the external nares or posterior pharynx is highly suggestive of sinusitis. Blockage of sinus drainage may prevent visualization of purulent drainage.
- F. Facial tenderness, elicited by percussion, is an unreliable sign of sinusitis.

III. Laboratory Evaluation

- A. **Imaging.** Plain films are usually unnecessary for evaluating acute sinusitis because of high cost and relative insensitivity.
- B. **CT scanning** is useful if the diagnosis remains uncertain or if extra-sinus (usually orbital or intracranial) complications are suspected. CT scanning is nonspecific and may demonstrate sinus abnormalities in 87% of patients with colds (not sinusitis).
- C. **MRI** is useful when fungal infections or tumors are seriously considered.
- D. **Sinus aspiration** is an invasive procedure, and is not appropriate for routine use. Indications for aspiration:
 1. Complicated sinusitis
 2. Immunocompromise
 3. Failure to respond to multiple courses of empiric antibiotic therapy
 4. Severe symptoms
- E. Cultures of nasal secretions correlate poorly with results of sinus aspiration.

IV. Management of Sinusitis

A. Antibiotic Therapy for Sinusitis

1. Amoxicillin is first-line therapy in patients without penicillin allergy. Trimethoprim-sulfamethoxazole is an alternative for penicillin-allergic patients.
2. A 2-3 week course of therapy is recommended; however, if the patient is improved but still symptomatic at the end of the course, the medication is continued for an additional 5 to 7 days after symptoms completely subside.

3. First-line Agents

- a. Amoxicillin (Amoxil): Adults, 500 mg tid orally for 14 days. Children, 40 mg/kg/d in 3 divided doses.
- b. Trimethoprim/sulfamethoxazole (Bactrim, Septra): Adults, 1 DS tab (160/800 mg) bid. Children, 8/40 mg/kg/d bid.
- c. Erythromycin/sulfisoxazole (Pediazole): Children, 50/150 mg/kg/d qid (maximum: 6 g/d).

4. Broader-Spectrum Agents

- a. Amoxicillin/clavulanate (Augmentin): Adults, 250 mg tid or 875 mg bid. Children, 40 mg/kg/d in 3 divided doses.
- b. Cefuroxime axetil (Ceftin): Adults, 250 mg bid. Children, 125-250 mg bid.
- c. Cefixime (Suprax): Adults, 200 mg bid. Children, 8 mg/kg/d bid.
- d. Cefpodoxime (Vantin) 200 mg bid
- e. Clarithromycin (Biaxin): 500 mg bid.
- f. Loracarbef (Lorabid): 400 mg bid.

30 Sinusitis

- g. Azithromycin (Zithromax) 500 mg as a single dose on day 1; 250 mg as a single dose on days 2-5

5. Indications for Use of a Broader-Spectrum Agent

- a. Failure to respond to amoxicillin
- b. High prevalence of beta-lactamase-producing *H influenzae* or *M catarrhalis*.
- c. Frontal or sphenoidal sinusitis
- d. Immunocompromise
- e. Chronic sinusitis

B. Fluoroquinolones have relatively poor activity against gram-positive organisms (eg, pneumococci), and they should not be used.

C. **Refractory Sinusitis:** If response to antibiotics is unsatisfactory, beta-lactamase-producing bacteria are likely to be present, and broad-spectrum therapy is required.

D. **Chronic Sinusitis** is commonly caused by anaerobic organisms. 3-4 weeks of therapy or longer is required.

E. Nasal Corticosteroids

- 1. Intranasal corticosteroids are an important adjunct to antibiotics because they reduce inflammation of the sinus ostia and restore sinus mucus drainage.
- 2. Nasal steroids inhibit the allergic inflammatory response and promote drainage of the sinuses.
- 3. Beclomethasone (Beconase AQ) AQ with 84 mcg/inhalation 2 sprays qd, or AQ or MDI in 42 mcg/inhalation 2 sprays bid.
- 4. Flunisolide (Nasalide AQ) 2 sprays bid.
- 5. Triamcinolone acetonide (Nasacort AQ or MDI) 2 sprays bid.
- 6. Budesonide (Rhinacort MDI) 2 puffs in each nostril bid.
- 7. Fluticasone (Flonase AQ) 2 sprays per nostril bid.
- 8. Beclomethasone dipropionate administered in a double-strength formulation (84 mcg/spray) given once a day is as effective and as well tolerated as beclomethasone regular-strength (42 mcg/spray). The double-strength formulation is as safe and as effective in children as the regular-strength formulation.
- 9. The topical nasal steroids are available as an aqueous solution or a dry aerosol preparation.
- 10. Localized and manageable side effects, such as nasal burning and stinging, sneezing, throat irritation, and drying of the mucous membranes, may occur.

F. Ancillary Treatments

- 1. **Steam and Saline** improves drainage of mucus. Spray saline (NaSal) or a bulb syringe with a saline solution (1 tsp of salt in 1 qt of warm water) may be used.
- 2. **Decongestants**
 - a. Topical or systemic decongestants may be used in acute or chronic sinusitis, including phenylephrine (Neo-Synephrine) or oxymetazoline (Afrin) nasal drops or sprays.
 - b. Oral decongestants, such as phenylephrine or pseudoephedrine, are active in areas not reached by topical agents.

V. Complications

- A. Bacterial sinus infection can sometimes spread to the eyes or brain, causing blindness and death.
- B. Swelling and redness around an eye, altered mentation, or a high fever raise the suspicion of a possible complication of bacterial sinusitis.
- C. **Meningitis, epidural abscess, subdural empyema, or brain abscess** are characterized by high fever and CNS symptoms.
- D. **Orbital cellulitis and abscess** are characterized by severe eye swelling and redness.
- E. Cavernous sinus thrombosis is characterized by bilateral eye findings and edema over the mastoid emissary vein, altered mentation and

meningismus.

- F. Mucocoele formation is a potential complication of chronic sinusitis, characterized by headache, proptosis, and diplopia. It occurs most often in the frontal sinuses. Symptomatic lesions generally require surgical intervention.

References: See page 148.

Pharyngitis

Labs: Throat culture, rapid antigen test.

Treatment:

Streptococcal Pharyngitis:

- Penicillin G Benzathine Suspension (Bicillin L-A) 1.2 million units IM x 1 dose.
- Penicillin V 250 mg PO qid x 10 days [250, 500 mg].
- Erythromycin base 250 mg PO qid; or enteric coated delayed release tablet 333 mg tid or 500 mg bid [250, 333, 500 mg]
- Erythromycin ethyl succinate (EES) 400 qid or 800 mg bid [400 mg].
- Clarithromycin (Biaxin) 250-500 bid [250, 500 mg].

Refractory Pharyngitis:

- Amoxicillin/clavulanate (Augmentin) 250 mg tid or 875 mg bid [250, 500, 875 mg].
- Dicloxacillin 250-500 mg qid [125, 250, 500 mg].
- Cephalexin (Keflex) 250-500 mg qid [250, 500 mg].

Prophylaxis:

- Penicillin V 250 qd.

Management of the HIV-Infected Patient

I. Initial Diagnostic Testing of Newly Diagnosed HIV Patients

- A. Complete blood cell count with differential and platelet counts. Repeat with each CD4 count
- B. Baseline liver and renal function tests, electrolyte panel
- C. Purified protein derivative (PPD 5 tuberculin units) 0.1 mL intradermal energy battery interpreted within 48 to 72 hours
- D. VDRL or RPR for syphilis (confirmed by a fluorescent treponemal antibody absorption test)
- E. Genital sexually transmitted disease testing for gonorrhea and chlamydia.
- F. CD4 T-cell count
- G. HIV RNA viral load level
- H. Hepatitis B screen (hepatitis B surface antigen, hepatitis B antibodies); if negative, consider vaccine
- I. Toxoplasmosis titer
- J. Chest X-ray
- K. Papanicolaou smear in women. Repeat every 6 mo. If two are sequentially normal, annually. If CD4 cell count <400 cells/mcL, every 6 mo.

II. Treatment

A. Antiretroviral Therapy

1. Combination with 3 agents is recommended. Two nucleoside analogs in combination with a protease inhibitor is recommended as initial therapy.
2. **Nucleoside Analogs**
 - a. Zidovudine (Retrovir, AZT) 200 mg tid [100, 200 mg caps, 50 mg/5 mL syrup]. Monitor for granulocytopenia, anemia.
 - b. Lamivudine (Epiriv, 3TC) 150 mg twice daily [150 mg].
 - c. Didanosine (Videx, ddl) 200 mg bid for patients >60 kg; or 125 mg bid for patients <60 kg. The powder is more palatable if taken with

32 Diverticulitis

ice-cold water [chewable tabs: 25, 50, 100, 150 mg; pwd 100, 167, 250 mg packets].

d. Stavudine (Zerit, D4T) 20 mg twice daily [15-mg, 20-mg, 30-mg and 40-mg capsules].

e. Zalcitabine (Hivid, ddC) 0.75 mg tid [0.375, 0.75].

3. Protease Inhibitors

a. Indinavir (Crixivan) 800 mg q8h [200, 400 mg].

b. Saquinavir (Invirase) 600 mg TID with a full meal [Cap 200 mg].

c. Ritonavir (Norvir) 600 mg with food twice daily with food [100 mg, 80 mg/dL]

d. Nelfinavir 750 mg PO tid [250 mg].

4. Non-Nucleoside Reverse Transcriptase Inhibitors

a. Nevirapine (Viramune) 200 mg qd x 2 weeks, then bid [200-mg].

b. Delavirdine (U-90) 400 mg three times daily; investigational.

B. Postexposure Prophylaxis

1. **Wound Decontamination.** The injury should be immediately washed and scrubbed with soap and water.

2. Zidovudine 200 mg PO tid, plus lamivudine (3TC) 150 mg PO bid for 4 weeks, plus indinavir, 800 mg PO tid for highest risk exposures. Treatment is begun as soon as possible after exposure.

C. PCP Prophylaxis (previous PCP, CD4<200)

1. TMP/SMX SS (80/400 mg) 1 tab PO qd **OR**

2. Dapsone 50 mg PO qd, or 100 mg twice weekly [100 mg].

3. Pentamidine, 300 mg in 6 mL sterile water via Respigard II nebulizer over 20-30min q4 weeks **OR**

D. Toxoplasmosis Prophylaxis

1. Primary prophylaxis is indicated for patients with positive antibodies to toxoplasmosis when the CD4 count drops below 100 cells/ μ L. TMP/SMX and dapsone are both active against PCP and also provide prophylaxis against toxoplasmosis.

E. Mycobacterium Avium Complex Prophylaxis

1. Approved for HIV-infected patients with CD4 counts <100/ μ L.

2. Prophylaxis consists of clarithromycin (Biaxin) (500 mg bid), or azithromycin (Zithromax) 1200 mg once a week.

F. Vaccinations

1. Pneumococcal vaccination(23) 0.5 mL IM or SQ once in life.

2. Hepatitis B vaccine (Recombivax HB, Heptavax B, Engerix B) if non-hepatitis immune, 1 mL IM/SC, repeat in 1 and 6 months.

References: See page 148.

Diverticulitis

I. Pathogenesis

A. By age 50 one third of adults have diverticulosis coli; approximately two thirds have diverticulitis by age 80. Ten to 20% of patients with diverticulosis will have complications of diverticulitis or diverticular hemorrhage.

B. **Causes of Diverticulosis:** Aging, elevation of colonic intraluminal pressure, and decreased dietary fiber. Diverticula occur where nutrient arteries penetrate the muscularis propria. Eighty-five percent are found in the sigmoid colon.

II. Clinical Presentation of Diverticulitis

A. Diverticulitis is characterized by abrupt onset of unremitting left-lower quadrant abdominal pain, fever, and an alteration in bowel pattern. Diverticulitis of the transverse colon may simulate ulcer pain; diverticulitis of the cecum and redundant sigmoid may resemble appendicitis. Right sided diverticulosis is more common among Asians (>75%) than among

Europeans.

B. Frank rectal bleeding is usually not seen with diverticulitis.

C. Physical Exam. Left-lower quadrant tenderness. Abdominal examination is often deceptively unremarkable in the elderly and in persons taking corticosteroids. Leukocytosis may occur.

Differential Diagnosis

Elderly	Middle Aged and Young
Ischemic colitis Carcinoma Volvulus Colonic Obstruction Penetrating ulcer Nephrolithiasis/urosepsis	Appendicitis Salpingitis Inflammatory bowel disease Penetrating ulcer Urosepsis

III. Diagnostic Evaluation

- A. Plain X-rays** may show ileus, obstruction, mass effect, ischemia, perforation.
- B. CT scan** is the test of choice to evaluate acute diverticulitis; used for staging the degree of complications and ruling out other diseases.
- C. Contrast Enema.** Water soluble contrast is safe, and useful in mild-to-moderate cases of diverticulitis when the diagnosis is in doubt.
- D. Endoscopy.** Acute diverticulitis is a relative contraindication--exclude perforation first. Used when the diagnosis is in doubt to exclude the possibility of ischemic bowel, Crohn's disease, or carcinoma.
- E. Ultrasound** occasionally is helpful to evaluate acute diverticulitis, although intestinal gas often interferes with the exam.
- F. Complete Blood Count** may show leukocytosis

IV. Treatment

A. Outpatient Treatment

1. Clear liquid diet
2. Oral antibiotics
 - a. Ciprofloxacin (Cipro) 500 mg PO bid AND
 - b. Metronidazole (Flagyl), 500 mg PO qid.

B. Inpatient Treatment

1. Severe cases should be hospitalized for gastrointestinal tract rest (NPO), intravenous fluid hydration, correction of electrolyte abnormalities, and antibiotics.
2. Nasogastric suction is initiated if the patient is vomiting or if there is abdominal distention.
3. Antibiotic coverage for enteric gram-negative and anaerobic organisms
 - a. Ampicillin 1-2 gm IV q4-6h AND
 - b. Gentamicin or tobramycin 100-120 mg IV (1.5-2 mg/kg), then 80 mg IV q8h (5 mg/kg/d) AND
 - c. Metronidazole (Flagyl) 500 mg q6-8h (15-30 mg/kg/d) or Clindamycin (Cleocin) 600-900 mg IV q8h for more severe disease.
 - d. Monotherapy with second-generation cephalosporin (eg, cefoxitin, cefotetan) or extended-spectrum penicillins (eg, piperacillin-tazobactam, ampicillin-sulbactam) may be used.
- C.** Frequently reassess the abdomen for the first 48-72 hours. Improvement should occur over 48-72 hours with decreased fever, leukocytosis, and abdominal pain. Failure to improve or deterioration are indications for reevaluation and consideration of surgery. Analgesics are avoided because they may mask acute deterioration, and they may obscure the need for urgent operation.
- D.** Oral antibiotics should be continued for 1-2 weeks after resolution of the

34 Diverticulitis

acute attack. Ciprofloxacin, 500 mg PO bid.

- E. After the acute attack has resolved, clear liquids should be initiated, followed by a low residue diet for 1-2 weeks. Then change to a high-fiber diet with psyllium.

V. Complications of Diverticulitis

A. Fistula Formation

1. With repeated attacks of diverticulitis, a fistulous tract can form between bowel, urinary bladder, integument, pelvic floor, or vagina.
2. Colovesical fistula is the most common. Pneumaturia and recurrent urinary tract infections, characterized by multiple organisms may occur. Reflux of contrast into the urinary bladder during contrast enema confirms the diagnosis.
3. A segmental colon resection is usually performed after the acute diverticulitis has resolved.

- B. **Intestinal Obstruction.** After repeated episodes of diverticulitis, the colon becomes fixed, fibrotic, stenosed, and obstruction may result. Surgical resection is indicated.

C. Abscess

1. If no response to medical therapy within 24-48 hours, or if an abdominal mass is palpable, consider the possibility of an intra-abdominal abscess, and obtain an abdominal CT scan.
2. Obtain early surgical consultation for percutaneous drainage followed by surgical drainage.

D. Perforation and Peritonitis

1. Diverticular perforation will result in peritonitis.
2. Pain becomes severe, with peritoneal signs (guarding, rebound tenderness, rigidity), fever, tachycardia, elevation of white blood count. Most patients are toxic and require prompt surgical intervention.
3. Perforation is indicated by free peritoneal air that may be visible below diaphragm on a chest x-ray. Perforated viscus from an ulcer is a much more common cause of free air.

VI. Surgical Therapy

- A. An emergency sigmoid colectomy with proximal colostomy is indicated for attacks of diverticulitis associated with sepsis, peritonitis, obstruction, or perforation.

- B. Elective sigmoid resection is indicated for second or subsequent attacks of diverticulitis, or for attacks with complications managed nonoperatively (eg, percutaneous CT-guided drainage of an abscess), or if carcinoma, or a single episode in a young patient (<40-50 years old), or an immunosuppressed patient.

C. Operative Procedures

1. **Single Stage Procedure.** This procedure is usually performed as an elective procedure after resolution of the acute attack of diverticulitis. The segment containing inflamed diverticulum (usually sigmoid colon) is resected with primary anastomosis. A bowel prep is required.
2. **Two Stage Procedure.** This procedure is indicated for acute diverticulitis with obstruction or perforation with an unprepared bowel. The first stage consists of resection of the involved segment of colon, with end colostomy and either a mucous fistula or a Hartmann rectal pouch. The second stage consists of a colostomy take-down and reanastomosis after 2-3 months.
3. **Percutaneous Drainage of Diverticular Abscess.** CT guided drainage of accessible, well-circumscribed abscess cavities can be performed. A one-stage resection is done later as an elective procedure.

References: See page 148.

Urinary Tract Infection

I. Clinical Evaluation

- A. Acute Uncomplicated Lower Tract Infection** is associated with dysuria, urgency, and frequency without fever or back pain. Lower tract infections are most common in women in their childbearing years. Internal dysuria indicates bladder infection, external dysuria indicates vaginitis.
- B. Acute Pyelonephritis** is associated with fever and costovertebral angle pain and tenderness with frequency, urgency, and dysuria. Leukocytosis is often present; urinalysis reveals pyuria and bacteriuria.

II. Pathogenesis of Urinary Tract Infection

- A.** Enterobacteriaceae are the bacteria most often responsible. *Escherichia coli* causes 80% of urinary tract infections. *Staphylococcus saprophyticus* (Gram-positive, coagulase-negative) is the second most common, particularly in young women; the diagnosis is often missed due to low urine colony counts and negative nitrite screening.
- B.** *Chlamydia trachomatis* infection may cause dysuria, urgency, frequency, pyuria, and sterile bacterial cultures; diagnosis is by cell culture or monoclonal antibody techniques of urethral or cervical exudate.
- C. Risk Factors for Urinary Tract Infection.** Diaphragm or spermicide use (alters vaginal pH), sexual intercourse, elderly, anatomic obstruction, calculi.

III. Laboratory Evaluation

- A.** Microscopic pyuria is a nonspecific indicator of inflammation; bacteriuria confirms the diagnosis. Bacteria on microscopic examination of unspun urine correlates well with UTI.
- B.** Positive nitrite reading is a useful test, but false-negatives occur. False-negative and false-positives may also be seen with leukocyte esterase.
- C.** Culture and sensitivity testing is indicated if there is failure to respond to therapy, suspected acute pyelonephritis, or complicated infections (calculi, obstruction, diabetes, immunosuppression).
- D.** Follow-up post treatment culture is indicated in pyelonephritis or complicated infections. Recurrence or persistence of the same organism indicates a residual focus of infection.

IV. Treatment of Lower Urinary Tract Infection

- A. Acute uncomplicated urinary tract infections** can be treated with oral trimethoprim-sulfamethoxazole. A good alternative would be a fluoroquinolone. Other alternatives include an oral cephalosporin or amoxicillin, but many pathogens are resistant to amoxicillin.
- B. Complicated urinary tract infections** that occur repeatedly after the use of antimicrobial agents or that are acquired in hospitals are more likely to be due to antibiotic-resistant gram-negative bacilli. In more severely ill patients, treatment with a third-generation cephalosporin, ticarcillin/clavulanic acid, piperacillin/tazobactam or imipenem is recommended, sometimes together with an aminoglycoside, especially if urosepsis is present.
- C. A 3-day course** is recommended for uncomplicated cystitis. A 7 day course is indicated if diabetes, symptoms >7 days, or elderly.
 1. Trimethoprim-sulfamethoxazole (Septra) 1 double strength tab (160/800 mg) PO bid.
 2. Norfloxacin (Noroxin) 400 mg PO bid.
 3. Ciprofloxacin (Cipro) 250 mg PO bid.
 4. Ofloxacin (Floxin) 400 mg PO bid.
 5. Lomefloxacin (Maxaquin) 400 mg PO qd.
 6. Levofloxacin (Levaquin) 250 mg PO qd.
 7. Cefadroxil (Duricef) 500 mg PO bid.
 8. Cephalothin (Keflex) 500 mg PO q6h.
 9. Cefixime (Suprax) 200 mg PO bid or 400 mg PO qd.
 10. Cefazolin (Ancef) 1-2 gm IV q8h.
 11. Nitrofurantoin (Macrobid) 100 mg PO qid [100 mg] or Macrobid 100

36 Urinary Tract Infection

mg PO bid [100 mg].

12. Amoxicillin/clavulanate (Augmentin) 250 mg PO tid.

D. Urinary Analgesia. Phenazopyridine (Pyridium) 100 mg PO tid [100 mg]

V. Treatment of Acute Pyelonephritis

A. Parenteral antibiotics are indicated in older patients, coexistent illness (diabetes, heart disease), or for ill appearing patients.

B. Otherwise healthy, patients with uncomplicated pyelonephritis without signs of sepsis can be treated with oral trimethoprim-sulfamethoxazole. A good alternative would be an oral fluoroquinolone or an oral cephalosporin.

C. In more severely ill patients, treatment with an IV third-generation cephalosporin, ticarcillin/clavulanic acid, piperacillin/tazobactam, or imipenem is recommended, sometimes together with an aminoglycoside, especially if urosepsis is present.

D. Coverage should include gram-negative organisms and enterococci. E coli resistance to ampicillin and trimethoprim/sulfamethoxazole is increasing.

E. Antibiotic Therapy for Uncomplicated Acute Pyelonephritis

1. Treatment should be continued for 10-14 days.

2. Trimethoprim-sulfamethoxazole (Septra) 1 double strength tab (160/800 mg) PO bid or 10 mLs in 100 mLs D5W IV over two hours q12h.

3. Ciprofloxacin (Cipro) 250-500 mg PO bid or 200-400 mg IV q12h.

4. Norfloxacin (Noroxin) 400 mg PO bid.

5. Ofloxacin (Floxin) 200-400 mg PO or IV q12h.

6. Lomefloxacin (Maxaquin) 400 mg PO qd.

7. Levofloxacin (Levaquin) 250 mg PO qd.

8. Cefadroxil (Duricef) 500 mg PO bid.

9. Amoxicillin/clavulanate (Augmentin) 500 mg tab PO tid.

10. Ceftizoxime (Cefizox) 1 gm IV q8h.

11. Ceftazidime (Fortaz) 1 gm IV q8h.

12. Piperacillin/tazobactam (Zosyn) 3.375-4.5 gm IV/PB q6h.

13. Ampicillin 1 gm IV q4-6h **AND**

14. Gentamicin or tobramycin - loading dose of 100-120 mg IV (2 mg/kg); then 1.5 mg/kg IV q8h

F. Antibiotic Therapy for Complicated Acute Pyelonephritis

1. Ticarcillin/clavulanate (Timentin) 3.2 gm IV q8h.

2. Imipenem/cilastatin (Primaxin) 250-500 mg IV q6-8h.

G. Parenteral therapy should be continued for 24 hours after afebrile; oral agents should be taken to complete a 10-14 day course. If fever does not respond within 72 hours, imaging studies should be obtained to exclude obstruction, calculi, or abscesses.

VI. Recurrent Urinary Tract Infections

A. If recurrent UTI's occur, use of a diaphragm and spermicide should be discontinued, and postcoital voiding and long-term, single-dose, antimicrobial therapy may be used.

B. Long-term Suppressive Therapy. Trimethoprim/sulfamethoxazole (Bactrim, Septra), single-strength tablet 3 times weekly.

C. Self administration of a single-dose or short-term antibiotic such as trimethoprim/sulfamethoxazole may be prescribed.

VII. Indwelling Catheters

A. Antibiotic prophylaxis is not recommended while the catheter is in place; antibiotics are reserved for symptomatic infection or sepsis.

B. Bacteriuria that is acquired after short-term catheter use should be treated.

References: See page 148.

Herpes Simplex Virus Infections

I. Pathogenesis of Herpes Simplex

- A. Any mucocutaneous surface or visceral site may be infected by HSV. Two strains of the virus, herpes simplex virus type 1 (HSV-1) and herpes simplex virus type 2 (HSV-2), cause clinically indistinguishable lesions.
- B. Both HSV-1 and HSV-2 may cause genital and orofacial lesions. In genital infections, recurrences are more commonly caused by HSV-2 than HSV-1.
- C. Primary HSV infection occurs after first exposure, followed by a latency period while the virus remains dormant within the nerve ganglion.
- D. Antibody studies have shown that 60% of all US adults are positive. The incubation period for primary HSV infections is 1-26 days.

II. Clinical Features

A. Diagnostic Features of HSV Infection

1. Grouped vesicles or a solitary vesicle with erythematous bases, progressing to ulceration.
 2. Primary infections may be accompanied by flu-like symptoms.
 3. Prodromal burning or itching (in recurrent disease)
 4. Lesions are painful and persist for several days forming a honey-colored crust. Healing is usually complete within 3 weeks.
- B. Immunosuppressed patients, especially HIV infected patients, have more frequent and more severe infections.
 - C. Contact with ulcerative lesions or with secretions may result in transmission. Asymptomatic viral shedding may also cause infection.
 - D. **Recurrent Disease**
 1. Ninety percent of symptomatic HSV-2 infections and 60% of HSV-1 infections recur within 1 year. Patients usually experience 5-8 recurrences per year, but some may have outbreaks as frequently as every 2-3 weeks. The frequency and number of recurrences are highly variable.
 2. Recurrent lesions usually arise at the site of the primary infection. Over time, the recurrences become less frequent.
 3. Reported precipitating events for recurrent infection include menstruation, stress, sun exposure, cold, and local trauma.
 4. Sunscreen and lip balm are recommended.
 - E. HSV should be suspected as a cause of urethritis in men if dysuria is out of proportion to the urethral discharge.

III. Laboratory Tests

- A. Diagnosis of genital herpes requires the characteristic history and physical appearance of lesions plus the selective use of viral culture or immunofluorescent assay.
- B. Viral culture requires 48-96 hours and has an accuracy rate of 85-90%.
- C. Immunofluorescent assays rapidly detects HSV in smears. Serologies are not useful since antibodies become permanently positive after infection.

Therapy for HSV Infections

Type of infection	Dosage/regimen	Considerations
Primary infection	Acyclovir (Zovirax) 400 mg PO tid x 10 days or Valacyclovir (Valtrex) 500 mg PO bid x 10 days or Famciclovir (Famvir) 125 mg PO bid x 10 days Acyclovir (Zovirax) 5 mg/kg IV q8h over one hour for 5-7 or until clinical resolution [Tab 400, 800 mg; cap 200]	<p>Preferred route in immunocompetent patients</p> <p>Only for severe symptoms or complications</p>

Recurrent Infection Episodic therapy	Acyclovir (Zovirax) 400 mg PO tid or 800 mg bid for 5 days or Valacyclovir (Valtrex) 500 mg PO bid for 5 days or Famciclovir (Famvir) 125 mg PO bid for 5 days	Treatment is most effective when initiated at the earliest sign of recurrence; it is of no benefit if initiated more than 48 hours after symptom onset
Suppressive therapy	Acyclovir (Zovirax) 400 mg orally bid	Indicated for patients with frequent and/or severe recurrences (>6 outbreaks per year)

D. Acyclovir (Zovirax)

1. Acyclovir is the drug of choice for the treatment and suppression of genital herpes. Acyclovir is virtually nontoxic to normal cells because only HSV-infected cells preferentially take in acyclovir.
2. **Side Effects.** Usually well tolerated, but nausea, vomiting, rash, or headache occur rarely.
3. Dosage should be reduced in renal insufficiency. Topical acyclovir is not effective.

E. Other Antivirals have more convenient bid dosing, but are more expensive than acyclovir and not more effective.

1. **Valacyclovir (Valtrex)** 500 mg bid x 5 days [500 mg]
2. **Famciclovir (Famvir)** 125 mg bid x 5 days.

F. Oral analgesics and sitz baths are useful. Keep area clean and dry with corn starch, baby powder, or a hair dryer. Pyridium may be useful for dysuria.

G. Serious or Life-Threatening HSV Infections require intravenous acyclovir.

H. Immunocompromised Patients

1. Treatment of genital herpes in the immunocompromised patient generally requires acyclovir therapy at higher doses and more frequent intervals.
2. Acyclovir, 400 mg, PO 3-5 times daily until clinical resolution. Double dose if no response in 3-5 days.

IV. Patient Counseling

- A. Patients should be warned about HSV autoinoculation from one body site to another. Infected areas should be patted dry rather than wiped dry.
- B. Patients are advised to abstain from sexual activity while lesions are present. Use of a latex condom is encouraged because of asymptomatic viral shedding.
- C. The risk of neonatal transmission must be explained to the patient.
- D. Recommended testing includes evaluation for gonorrhea, chlamydial infection, syphilis, genital warts, and human immunodeficiency virus (HIV).

V. Treatment of Recurrences

A. Episodic Acyclovir Therapy

1. Early initiation of therapy has been shown to produce a reduction in the duration of symptoms.
2. The patient should keep a supply of acyclovir and begin treatment at the earliest prodromal symptom in an attempt to abort an episode.

B. Suppressive Acyclovir Therapy

1. Suppressive acyclovir therapy has been shown to reduce the frequency of recurrence by 80% and to prevent recurrence in up to 30% of patients. Suppressive therapy is recommended when recurrences occur more than 6 per year.
2. A suppressive regimen could be used during periods of increased stress or when optimal protection is desired, such as during a vacation or before a wedding.

References: See page 148.

Herpes Zoster

I. Clinical Evaluation

- A. Zoster occurs in patients who have had chickenpox in the distant past. The disease occurs when the latent virus reactivates and causes a new, localized zoster rash.
- B. Zoster is usually heralded by dermatomal pain, sometimes accompanied by fever. Within a few days, the skin overlying the dermatome reddens and blisters. A few vesicles are usually grouped on one erythematous base, in contrast to the scattered, single vesicles of chickenpox. Several days later the vesicles become pustular and develop crusts, followed by scabs.
- C. Zoster may occur in any dermatome, but the thoracic dermatomes are most often affected. New lesions continue to appear for 2-3 days. Elderly patients are at greater risk for postherpetic neuralgia. In 90% of immunocompetent patients, pain eventually disappears completely.
- D. The frequency of zoster increases markedly after age 55, but people of any age can be affected.
- E. Less than 5% of immunocompetent patients who have one episode of herpes zoster will have another, and the episodes are usually separated by years. HIV-infected patients are more likely to have recurrent herpes infections.

F. Laboratory Evaluation

1. The diagnosis of herpes zoster can be made on clinical grounds without the need for laboratory tests.
2. Viral isolation and culture assays are not useful for varicella-zoster.
3. An isolated case of zoster in an apparently healthy young or middle-aged adult is probably not an indicator of an underlying immunodeficiency. HIV testing is considered when a patient who engages in high-risk behavior (sexual activities, drug use) develops zoster. Testing for HIV is also indicated when herpes zoster is protracted, recurrent, or involves multiple dermatomes.

G. Complications of Herpes Zoster

1. 15% of patients with zoster have involvement of the ophthalmic branch of the trigeminal nerve. Hutchinson's sign, a lesion on the tip of the nose, indicates corneal involvement; however, ophthalmic involvement may occur even in the absence of Hutchinson's sign. Treatment with IV acyclovir and topical agents is required to prevent blindness.
2. Disseminated herpes zoster is present when 20 or more lesions occur outside of the primary contiguous dermatomes. These patients are at risk for visceral dissemination.

II. Symptomatic Therapy for Zoster

- A. Wet dressings or compresses with Burow's solution (Domeboro) will protect sensitive areas.
- B. Calamine-containing lotions and creams and 10% salicylate (Aspercreme) are useful.
- C. Acetaminophen, nonsteroidal anti-inflammatory drugs, or analgesics with codeine (Vicodin) may be needed.

III. Antiviral Therapy for Zoster

- A. An antiviral can hasten the resolution of the rash by several days.
- B. Relief of acute pain occurs within two to three days after an antiviral is initiated. The duration of pain is reduced by about half.
- C. Antiviral therapy is more likely to be of benefit if initiated within 24 hours of rash onset.
- D. **Acyclovir (Zovirax)**
 1. 800 mg q4h while awake (5 times a day) for 7 days. [400, 800 mg tab].
 2. Oral acyclovir does not have significant adverse effects; nausea, headaches, diarrhea, and constipation may sometimes occur. Dosage

40 Syphilis

is adjusted in renal failure.

3. IV acyclovir is reserved for the severely immunosuppressed (bone marrow transplant patients) or for disseminated or ophthalmic zoster.
 4. The IV dose for zoster is 10 mg/kg, administered over a one-hour, q8h. Reduce dosage in renal failure. Nephrotoxicity can usually be avoided if the patient remains well-hydrated.
- E. **Famciclovir (Famvir)** for herpes zoster infections is equally effective to acyclovir; it has a more convenient dosing interval; one 500-mg tablet tid for 7 days.
- F. **Valacyclovir (Valtrex)**, 1,000 mg tid x 7 days [500 mg].
- G. **Foscarnet sodium (Foscavir)** is helpful for acyclovir-resistant herpes infections.
- H. Low-dose corticosteroids are not indicated because of the risk of potentiating the infection.
- I. Ophthalmic distribution zoster is a medical emergency which requires IV acyclovir and topical antivirals.
- IV. **Postherpetic neuralgia (PHN)** is the most common complication of herpes zoster. It is defined as chronic pain persisting for at least one month after the skin lesions have healed.
- A. The incidence of PHN is 5-50%. Those aged 60 and older have a 50% chance of developing PHN. PHN resolves within two months in about half of those affected.
- B. Antivirals, aspirin, and acetaminophen are not effective for PHN.
- C. **Topical Preparations:**
1. Capsaicin cream (Zostrix, Zostrix-HP) 0.025% tid-qid reduces the pain. Nonprescription ointments, such as Ben-Gay, Flex-all 454 or Aspercreme, may offer similar relief at lower cost.
 2. EMLA topical cream (lidocaine and prilocaine) qid may be useful.
 3. Amitriptyline (Elavil) is often effective; 10-25 mg qhs, increasing in weekly increments of 10-25 mg as needed.
 4. Transcutaneous electrical nerve stimulation (TENS), lidocaine injections, nerve block injections, permanent nerve blocks with alcohol, and nerve resectioning have been used.

References: See page 148.

Syphilis

Labs: VDRL/RPR (confirmed with FTABs or MHA), dark field microscopy; GC, chlamydia. HIV antibody.

Indications for CSF Examination Before Treatment:

- Neurologic or ophthalmic signs or symptoms
- Other evidence of active syphilis (e.g., aortitis, gumma, iritis)
- Treatment failure
- HIV infection
- Serum nontreponemal titer >1:32, unless duration of infection is known to be less than 1 year; or
- Nonpenicillin therapy planned, unless duration of infection is known to be greater than 1 year.

Treatment:

Primary, Secondary or Early Latent Disease if <1 year Duration:

- Penicillin G benzathine (Bicillin), 2.4 million units (1.2 MU IM in each buttock) one dose **OR**
- Doxycycline 100 mg bid x 14d [100 mg] **OR**
- Tetracycline 500 mg qid x 14d [250, 500 mg].

Treatment of Late Latent Syphilis or Latent Syphilis of Unknown Duration:

- Penicillin G Benzathine, 3 doses of 2.4 million units IM at 1-week intervals

Treatment of Neurosyphilis:

- Aqueous crystalline penicillin G, 12-24 million units daily, administered as 2-4

million units IV every 4 hours, for 10-14 days.

Follow-up Evaluation:

- Recheck VDRL at 3, 6, 12, 24 months. Ensure fourfold decrease by 3-4 months (primary, secondary) or 6-8 months (early latent). Test contacts and treat even if seronegative.

Tuberculosis

I. Pathophysiology of Tuberculosis

- In most individuals initially infected with mycobacterium tuberculosis (usually by respiratory aerosols), the primary pulmonary infection occurs early in life, and the organism is contained by host defenses. The primary infection usually resembles pneumonia or bronchitis, and the infection usually resolves without treatment.
- Later in life, the organism may escape immunological control and cause reactivation disease, usually pulmonary, but many anatomic sites can be involved (genitourinary system, bones, joints, meninges, brain, peritoneum, and the pericardium).

II. Diagnosis of Active Tuberculosis

- Diagnosis of active tuberculosis rests upon sputum examination for acid fast bacilli and subsequent culture and sensitivities. This process requires 4-6 weeks for identification and another 4-6 weeks for sensitivity testing.
- Tuberculosis is often the initial manifestation of HIV infection; serologic testing for HIV is recommended in all tuberculosis patients. Tuberculosis in HIV-infected patients is characterized by extrapulmonary disease in 70% of patients.

III. Treatment of Active Tuberculosis

- Suspected TB should be treated empirically with a 4 drug combination because of high rates of drug resistance.
- The four-drug regimen consists of isoniazid (INH), rifampin, pyrazinamide (PZA), and either ethambutol or streptomycin. A modified regimen is recommended for patients known to have INH-resistant TB.
- All patients diagnosed with TB now must be treated for 8 weeks with the four-drug regimen, followed by 18 weeks of INH and rifampin.
- The same approach should be used in both HIV-positive and HIV-negative patients.
- If multi-drug resistant TB (resistant to both INH and RIF) is encountered, therapy should be more prolonged and guided by antibiotic sensitivities.
- Vitamin B6 (pyridoxine) should be added for malnourished patients taking INH.
- Directly observed therapy, usually on a twice per week basis, should be instituted in situations where compliance is questioned.

Tuberculostatic Drugs

Isoniazid	5-10 mg/kg (300 mg) qd	Hepatitis, peripheral neuropathy
Rifampin	10-15 mg/kg (600 mg) qd	Hepatitis, purpura
Pyrazinamide	25 mg/kg (max 2 g) qd	Hepatotoxicity, skin rash
Ethambutol	15-25 mg/kg (max 2.5 g) qd	Retrolubar neuritis, skin rash

H. Combination Preparations

- Rifamate (isoniazid 150 mg and rifampin 300 mg); 2 capsules qd.

42 Tuberculosis

- 2. Rifater (isoniazid 50 mg/rifampin 120 mg/pyrazinamide 300 mg) 6 tablets qd; adjust dose for weight.

I. Clinical Monitoring

- 1. Symptoms improve within 4 weeks, and sputum cultures become negative within 3 months in patients receiving effective antituberculosis therapy. Delayed resolution of symptoms or persistently positive cultures indicate noncompliance or drug-resistance.
- 2. Sputum cultures should be obtained monthly until they are negative and after completion of therapy. Obtain a chest x-ray after 2-3 months and after completion of treatment to assess efficacy.

J. Monitoring for Drug Toxicity

- 1. Isoniazid, rifampin, and pyrazinamide are potentially hepatotoxic.
- 2. If transaminase levels increase to more than 5 times the upper limit of normal, isoniazid, rifampin, and pyrazinamide should be discontinued and alternative agents substituted.
- 3. Optic neuritis can result from ethambutol, and monthly red/green vision and acuity testing is necessary.

IV. Skin Testing for Tuberculosis

- A. Skin testing with purified protein derivative (PPD) has limited usefulness in determining the presence of active disease, but it is useful in detecting patients who are harboring latent tuberculosis who may need "prophylactic" therapy.
- B. A reactive tuberculin skin test supports the diagnosis of tuberculosis, but it is not specific.
- C. The test is read at 48 hrs and must be interpreted in combination with clinical and historical information.

Criteria for a Positive Tuberculin Skin Test

Induration >5 mm	Induration ≥10 mm	Induration ≥15 mm
Persons with HIV infection Close contacts of persons with infectious tuberculosis Persons with fibrotic lesions apparent on chest radiograph Immunosuppressed patients	Homeless, indigent persons Immigrants from endemic areas Persons with prior BCG vaccination, renal failure, diabetes, chronic pulmonary disease Prisoners, intravenous drug users, health care workers, alcoholics	Persons at low risk for tuberculosis

- D. A history of vaccination with bacille Calmette-Guerin (BCG) should be ignored in interpreting the results of tuberculin skin testing, because skin test reactivity from the vaccine declines by adulthood.

V. Chemoprophylaxis

- A. Chemoprophylaxis with isoniazid (INH) greatly decreases the likelihood of progression of latent tuberculous infection to active disease.
- B. Before administration of chemoprophylaxis, active tuberculosis must be excluded clinically and by chest x-ray because inadvertent use of isoniazid alone in active tuberculosis may induce drug resistance.
- C. Prophylaxis with INH is given for 6-9 months.
- D. In situations of exposure to INH resistant organisms, prophylaxis may be attempted with RIF and EMB for 12 months.
- E. If age greater than 35, liver function tests should be measured initially and monthly while on INH.

References: See page 148.

Tetanus Prophylaxis

History of Two Primary Immunizations:

Low risk wound - Tetanus toxoid 0.5 mL IM.

Tetanus prone - Tetanus toxoid 0.5 mL IM + Tetanus immunoglobulin (TIG) 250-500 U IM.

Three Primary & 10 yrs since last Booster:

Low risk wound - Tetanus toxoid, 0.5 mL IM.

Tetanus prone - Tetanus toxoid, 0.5 mL IM.

Three Primary & 5-10 yrs since last Booster:

Low risk wound - None

Tetanus prone - Tetanus toxoid, 0.5 mL IM.

Three Primary & ≤ 5 yrs since last Booster:

Low risk wound - None

Tetanus prone - None

Infectious Conjunctivitis

I. Clinical Evaluation of Conjunctivitis

- A. Infectious conjunctivitis is one of the most common causes of red eye. Infectious conjunctivitis may be sight threatening, such as with infection with herpes simplex or in gonococcal keratoconjunctivitis.
- B. **Symptoms:** Redness, foreign body sensation, itching, burning, tearing, discharge, and eyelid heaviness.
- C. **Significant Visual Loss, Photophobia, or Pain** suggests corneal or intraocular involvement.
- D. **Exposure History:** Recent contact with an individual with red eye indicates possible adenoviral conjunctivitis.
- E. **Systemic Illnesses or Symptoms** suggests viral conjunctivitis (adenovirus, herpes simplex, or infectious mononucleosis).

II. Examination of the Eye

- A. Visual acuity for each eye should be tested before examination. Check for eyelid swelling, erythema, discharge. Lid vesicles or ulcers indicate primary herpes simplex conjunctivitis.
- B. **Conjunctivitis with Follicles** suggests viral etiology, usually adenovirus and, occasionally, primary herpes simplex or chlamydia.
- C. **Fluorescein:** Place in the eye following the instillation of a topical anesthetic. A cobalt blue light will reveal fluorescence, indicating abrasion, corneal ulcer, or herpes simplex dendritic lesions.
- D. **Preauricular and Submandibular adenopathy** indicates viral conjunctivitis (adenovirus or herpes simplex), or bacterial conjunctivitis.
- E. **Bacterial Conjunctivitis:** Pseudomembrane or a membrane of exudate may be present.

III. Laboratory Studies

- A. **Cultures and Gram Stain:** Cultures and gram stain should be performed for neonatal conjunctivitis and in severe conjunctivitis.
- B. **Normal Flora of the Conjunctiva:** Staphylococcus epidermidis, Diphtheroids, and Staphylococcus aureus may be present on routine culture. Other organisms include S viridans, S pneumoniae, Moraxella, Propionibacterium acnes, Lactobacillus, Eubacterium, and Peptostreptococcus.

IV. Treatment of Bacterial Conjunctivitis

- A. Bacterial conjunctivitis is characterized by conjunctival hyperemia, lid edema, moderate-to-copious purulent discharge, chemosis, discomfort, and possibly pain. A pseudomembrane or membrane may be present.
- B. Symptoms are abrupt in onset and are usually present for less than a week.

C. Topical Antibiotics

1. Sulfacetamide 10 % (Bleph-10, Sulamyd), apply ointment to affected eyes qid and hs or 2 drops into eyes q2h.
2. Bacitracin ointment, apply into affected eye 1-3 times daily.
3. Gentamicin (Garamycin) solution, 0.3%, 2 drops in each eye qid for 7-10 days; or ophthalmic ointment 2-3 times a day.
4. Tobramycin (Tobrex), 1-2 drops into affected eyes q1-4h; or ophthalmic ointment 1/2 inch 2-3 times a day.
5. Erythromycin, apply ointment to affected eyes q4-6h.
6. Ciprofloxacin (Ciloxan), 1-2 drops into affected eyes q2h while awake for 2 days, then the q4h.
7. Norfloxacin, 1-2 drops qid.

D. Conjunctivitis due to *H. influenzae*, *N. gonorrhoeae*, and *N. meningitidis* requires systemic antibiotic therapy in addition to topical treatment.

E. **Topical steroids** are contraindicated in conjunctivitis because of the risk of potentiating infection.

F. Topical anesthetic agents should not be prescribed for ocular pain because they may cause severe local reactions, permanent scarring, and corneal damage.

G. **Contact Lenses:** Discontinue use of lenses until symptoms and signs have completely resolved. All ocular solutions should be discarded and lenses disinfected. The lenses or lens solution, may be cultured.

References: See page 148.

Gastrointestinal Disorders

Gastroesophageal Reflux Disease

One-third of the population experiences symptoms of heartburn at least monthly. The severity of gastroesophageal reflux disease (GERD) ranges from occasional mild symptoms to severe, erosive esophagitis with complications of ulcer, stricture, Barrett's esophagus, and hemorrhage.

I. Clinical Evaluation of Gastroesophageal Reflux Disease

- A. The most common symptom is heartburn, a burning sensation in the epigastric or retrosternal area, rising toward the throat, often occurring postprandially. Regurgitation, dysphagia, and belching may occur.
- B. Hoarseness, nocturnal cough, and wheezing may be caused by chronic reflux. Asthma may be exacerbated by GERD.
- C. Chronic reflux is associated with Barrett's esophagus (columnar metaplasia of esophageal mucosa) and may predispose to esophageal adenocarcinoma.
- D. GERD is caused by decreased lower esophageal sphincter (LES) pressure. Sphincter tone can be impaired by consumption of fatty foods and anticholinergic medications.

II. Therapeutic Approach to Gastroesophageal Reflux Disease

A. **Empiric Therapy:** When classic symptoms (heartburn) are present, a presumptive diagnosis of GERD may be made.

B. Non-Pharmacologic Therapy for Gastroesophageal Reflux Disease

1. **Initial treatment** consists of diet and lifestyle modifications and prn use of antacids. Lifestyle modifications include weight loss, reduced dietary fat, chocolate, peppermint, reduced size of meals; restriction of smoking and alcohol; elevation of the head of the bed; avoidance of recumbency for three hours after a meal; and avoidance of tight-fitting clothes.
2. The patient's medications should be reviewed for drugs that exacerbate GERD, including beta-agonists (eg, albuterol), theophylline, anticholinergics, calcium channel blockers, nitrates, estrogen, progesterone, meperidine, morphine, and nicotine.
3. When taking medications, patients should consume ample liquid.

C. Acid-Suppressive Treatment

1. Patients who continue to have symptoms should be offered acid-suppressive treatment or possibly a prokinetic drug. The four available H_2 -blockers are equally safe and effective. A twice-daily schedule should be used to provide 24-hour acid control.

Pharmacologic Treatment of Gastroesophageal Reflux Disease

Agent	Dosage	
Histamine-2 blockers: Inhibit gastric acid secretion		
Cimetidine (Tagamet) Ranitidine (Zantac) Famotidine (Pepcid) Nizatidine (Axid)	400-800 mg bid 150 mg bid-qid 20-40 mg bid 150 mg bid-qid	Cimetidine may cause impotence and gynecomastia; many drug interactions
Prokinetic drugs: Increase lower esophageal sphincter pressure, increase peristalsis		
Metoclopramide (Reglan)	10 mg qid	Neurologic and

Cisapride (Propulsid)	Up to 20 mg qid [10 mg]	Does not have neurologic or psychotropic side effects
H⁺,K⁺-ATPase (proton-pump) inhibitors: Inhibit gastric acid secretion		
Omeprazole (Prilosec) Lansoprazole (Prevacid)	20 mg qd or bid 30 mg qd	8 weeks of treatment

D. Promotility Drugs

1. Promotility drugs correct LES incompetence and delayed gastric emptying.
2. **Metoclopramide (Reglan)** 10 mg qid, produces relief, but poor tolerance reduces its use on a regular basis.
3. **Cisapride (Propulsid)** is also a promotility drug, but it has much greater tolerability than metoclopramide because it does not exhibit antidopaminergic effects and does not cross the blood-brain barrier. Most patients will continue to be treated initially with an H₂-blocker.

E. Persistent Symptoms

1. For patients with persistent symptoms following 6-8 weeks of drug therapy, or for patients initially presenting with dysphagia, hemorrhage, or severe disease, further diagnostic evaluation is necessary. Evaluation may include air contrast barium, esophageal endoscopy, biopsy, pH monitoring, or an esophageal motility study.
2. Treatment options for persistent symptoms include combination of an H₂-blocker with a promotility drug, double-dose H₂-blocker, or switching to omeprazole (Prilosec).
3. **Omeprazole (Prilosec)** is more effective than H₂-blockers in symptom relief (83%) and in healing of esophagitis (78%). Omeprazole is effective even in patients who have failed high doses of an H₂-blocker. The majority of patients will respond to omeprazole 20 mg qd. More than 20 mg bid is rarely required.

F. Recurrent or Refractory GERD

1. Patients who have frequent recurrences or who have an inadequate response to drug therapy are evaluated for maintenance therapy. The preferred method for maintenance treatment of GERD is omeprazole (Prilosec) 20 mg daily; this regimen is effective and safe in maintaining remission.
2. **Ranitidine (Zantac)** may be used for maintenance in a dose of 150 mg bid. Lansoprazole or cisapride may have a role in maintenance therapy.
3. **Anti-Reflux Surgery:** A small minority of patients with intractable disease are considered for antireflux surgery to reestablish a competent lower esophageal sphincter. Antireflux surgery has shown disappointing long-term results, and is indicated only on rare occasions.
 - a. **Nissen Fundoplication:** The fundus is completely wrapped around the esophagus, and the hiatus is closed. The procedure may be done laparoscopically. It is the most commonly used operation.
 - b. **Hill Procedure:** Fundic wrap and anchoring to pre-aortic fascia; the hiatus is closed.
 - c. **Belsey Procedure:** Exaggerated gastroesophageal junction angle in the stomach is anchored below diaphragm.
 - d. **Collis Gastroplasty:** A "tube" of gastric mucosa is created around the esophagus.

References: See page 148.

Peptic Ulcer Disease

I. Clinical Evaluation

- A. Peptic ulcer disease (PUD) is characterized by epigastric pain that may be exacerbated by fasting and relieved by food or antacids. Nausea and vomiting are common. Hematemesis ("coffee ground" emesis) or melena (black tarry stools) are indicative of significant bleeding.
- B. **Physical Examination.** Tenderness to deep palpation is often present in the epigastrium; stool is often guaiac-positive.
- C. *Helicobacter pylori* (HP) is the most frequent cause of PUD. Nonsteroidal anti-inflammatory drugs (NSAIDs), smoking, alcohol, and pathologically high acid-secreting states (Zollinger-Ellison syndrome) are less common causes.
- D. All patients with PUD and documented HP infection should be treated for HP during an active ulceration or while asymptomatic.
- E. Treatment of HP in patients with PUD significantly decreases the recurrence rate of PUD and virtually eliminates the need for maintenance therapy with acid-suppressive medications.

II. Detection of *Helicobacter Pylori* Infection

- A. Patients with symptoms of uncomplicated PUD should be evaluated with a non-endoscopic serologic antibody test for HP. Patients with complicated disease (eg, age >50, severe pain, upper GI bleeding) should receive endoscopy and biopsy for HP.
- B. **Non-endoscopic Tests (non-invasive)**
 1. Serologic testing for antibodies to HP (IgG and IgA), by ELISA quantitation or by immunoassay, has good sensitivity and specificity. These tests are used for initial screening; however, they are not useful to confirm eradication. The immunoassay is an easy to perform office procedure.
 2. **Labeled Urea Breath Tests.** ^{13}C -urea and ^{14}C -urea breath tests have high sensitivity and high specificity and are easy to perform in the office. They are useful, non-invasive tests to confirm eradication of HP 4 weeks after the completion of therapy.
- C. **Endoscopic Tests**
 1. Rapid urease tests (CLOtest, Pyloritek) have good sensitivity and specificity. The results are usually rapidly available.
 2. **Histologic Examination** give additional information about the degree of underlying inflammation or other mucosal abnormalities.
 3. **Culture** requires a microbiology lab with adequate experience. It is not usually needed except to check for resistant organisms.
- D. **Eradication** is usually assessed clinically by alleviation of symptoms. If symptoms recur, a urea breath test or endoscopic biopsy may be useful to confirm eradication.

III. Treatment of Peptic Ulcer Disease

- A. **Active Ulcer.** For patients with an active duodenal or gastric ulcer, acid suppression with a histamine-2 receptor antagonist or proton pump inhibitor is continued for a total of 4 to 8 weeks, with anti-HP therapy for the first 2 weeks.
- B. **Treatment Regimens for Elimination of *H. pylori***
 1. One week of therapy is recommended
 2. **Bismuth, Metronidazole, Tetracycline, Ranitidine**
 - a. 14 day therapy.
 - b. Bismuth (PeptoBismol) 2 tablets po qid.
 - c. Metronidazole (Flagyl) 250 mg po qid (tid if cannot tolerate the qid dosing).
 - d. Tetracycline 500 mg po qid (amoxicillin 500 mg po qid in children).
 - e. Ranitidine (Zantac) 150 mg PO bid.
 - f. Efficacy is greater than 90%; very inexpensive, proven efficacy in multiple studies, and moderate side-effects. Tetracycline is better

than amoxicillin unless contraindicated.

3. **Amoxicillin, Omeprazole, Clarithromycin (AOC)**

- a. 10 days of therapy.
- b. Amoxicillin 1 gm po bid.
- c. Omeprazole (Prilosec) 20 mg po bid.
- d. Clarithromycin (Biaxin) 500 mg po bid.
- e. Expensive, but usually well tolerated.

4. **Metronidazole, Omeprazole, Clarithromycin (MOC)**

- a. 10 days of therapy
- b. Metronidazole 500 mg po bid.
- c. Omeprazole (Prilosec) 20 mg po bid.
- d. Clarithromycin 500 mg po bid.
- e. Efficacy is >80%
- f. Expensive, usually well tolerated.

C. **Omeprazole, Clarithromycin (OC)**

1. 14 days of therapy.
2. Omeprazole (Prilosec) 40 mg po qd for 14 days, then 20 mg qd for and additional 14 days of therapy.
3. Clarithromycin 500 mg po tid.

D. **Ranitidine-Bismuth-Citrate, Clarithromycin (Rbc-C)**

1. 14 days of therapy.
2. Ranitidine-bismuth-citrate (Tritec) 400 mg po bid.
3. Clarithromycin 500 mg po tid.
4. Efficacy is 70-80%; expensive

E. **Follow-up Evaluation.** At least 4 weeks after completion of treatment, confirmation of HP eradication consists of a urea breath test or repeat endoscopy.

F. **Acute H₂-Blocker Therapy**

1. Cimetidine (Tagamet), 400 mg bid or 800 mg hs.
2. Ranitidine (Zantac), 150 mg bid or 300 mg hs.
3. Famotidine (Pepcid), 20 mg bid or 40 mg hs
4. Nizatidine (Axid Pulvules), 150 mg bid or 300 mg hs
5. Side effects are uncommon.
6. Maintenance therapy is one half of the therapeutic dose. If H. pylori therapy has been completed, most ulcers will not recur, and maintenance therapy will not be required.

G. **Mucosal Protective Agent--Sucralfate (Carafate)** is a mucosal, protective agent; 1 gm tid, before meals and hs; constipation is common; binds to other drugs.

H. **Proton Pump Inhibitors**

1. **Omeprazole (Prilosec)** is reserved for ulcers that are refractory to H₂ blockers and sucralfate. 20 mg qd. Side effects are rare.
2. **Lansoprazole (Prevacid).** 15 mg before breakfast qd.

IV. **Surgical Treatment of Peptic Ulcer Disease**

A. **Indications for Surgery.** Exsanguinating hemorrhage, >5 units transfusion in 24-hours, rebleeding during same hospitalization; intractability, perforation, gastric outlet obstruction, endoscopic signs predictive of rebleeding.

B. **Emergency Surgery for Peptic Ulcer Disease**

1. **Unstable Patients** should receive a truncal vagotomy, oversewing of bleeding ulcer bed, and a pyloroplasty.
2. **Stable Patients** should be managed with oversewing of the ulcer bed with either a vagotomy and antrectomy or a proximal gastric vagotomy.

C. **Surgical Therapy of Duodenal Ulcer Disease**

1. **Operative Therapy.** If the ulcer is still active after adequate medical therapy, surgery should be considered.
2. **Vagotomy Procedures**
 - a. Truncal vagotomy with drainage procedure (pyloroplasty or gastrojejunostomy).

b. Selective vagotomy with drainage procedure.

c. Proximal gastric (parietal cell, highly selective) vagotomy (usually without drainage procedure).

3. **Vagotomy and Antrectomy** with gastroduodenostomy (Billroth I) or gastrojejunostomy (Billroth II). Antrectomy consists of removal of distal one third of stomach.

D. **Surgical Therapy for Gastric Ulcer** consists of gastric resection to include ulcer. Vagotomy should be added in patients with increased acid secretion.

References: See page 148.

Constipation

Constipation affects about 2% of the population, occurring more frequently in persons older than 65. Many patients seek medical attention because they don't have a regular bowel movement every day, although their bowel movements are normal. These patients need only reassurance that they are normal.

I. Clinical Evaluation

A. Constipation is defined as the presence of 2 or more of the following:

1. Fewer than 3 bowel movements/week.
2. Excessive straining during bowel movements.
3. A feeling of incomplete evacuation after bowel movements.
4. Passage of hard or pellet-like stools.

B. Clinical Evaluation

1. Determine the time of onset of constipation, stool frequency and consistency, the degree of straining, sensation of complete or incomplete evacuation, or the need for digital disimpaction.
2. Chronic suppression of the urge to defecate contributes to constipation.
3. Determine the amount of fiber and fluid consumed. Assess obstetric, surgical and drug histories, back trauma or neurologic problems.

C. Physical Examination

1. A palpable colon with stool, particularly in the left lower quadrant, may be detected, although the examination is often normal. Gastrointestinal masses should be sought.
2. Perianal inspection may reveal skin excoriation, skin tags, anal fissures, anal fistula, or hemorrhoids.
3. Rectal examination may reveal a mass or stool. Resting and squeeze sphincter tone is assessed. When the patient is asked to bear down as if to defecate, relaxation of anal tone and perineal descent should be palpable. The absence of anal relaxation or inadequate perineal descent, raises the suspicion of obstructive defecation.

D. **Laboratory Evaluation.** A complete blood cell count, glucose, calcium, phosphate, thyroid function test, calcium, stool examination for ova and parasites, occult blood, and flexible sigmoidoscopy should be completed to exclude organic causes.

E. If the history, physical exam, or laboratory testing suggests a colonic structural abnormality, colonoscopy or barium enema is necessary to rule out colon cancer.

F. Secondary Causes of Constipation

1. Anatomic lesions (fissure in ano, hemorrhoids, fistulas, ischiorectal abscess), colonic neoplasms, hypothyroidism, hypercalcemia, diabetes, Hirschsprung's disease, Parkinson's disease, multiple sclerosis, or cerebrovascular disease may cause constipation.
2. Inadequate fiber intake commonly causes constipation.
3. Drugs that cause constipation include opiate analgesics, aluminum-containing antacids, iron and calcium supplements, antidiarrheals, antihistamines, antidepressants, antiparkinson agents, and antihypertensives (calcium channel blockers).

50 Constipation

- 4. If secondary causes have been excluded, the most likely cause is idiopathic constipation related to a disorder of colorectal motility.

II. Empiric Management of Constipation

- A. **Behavioral Modification.** The patient should be encouraged to heed the urge to defecate and not suppress it. Patients should establish a regular pattern of moving their bowels at the same time every day, usually in the morning, after breakfast. Daily exercise is advised
- B. **Fiber.** If no obvious cause has been found, the patient is placed on a diet of 20-30 g of dietary fiber per day. Fiber must be taken with ample fluids, otherwise constipation may worsen. Fiber often produces bloating, flatulence, and distention during the first few weeks of treatment.
- C. Laxatives and nonessential drugs are discontinued.

Fiber Preparations

Preparation	Recommended Dose	Doses per Day (with 8 oz liquid)
Powder Metamucil (regular)	1 tsp	1-3
Metamucil (orange flavor or sugar-free)	1 tsp	1-3
Citrucel (orange flavor or sugar-free)	1 tbsp	1-3
Fiberall Natural Flavor	1 tsp	1-3
Wafers Metamucil	2	1-3
Tablets Fiberall	1	1-2
Chewable FiberCon	2	1-4

III. Secondary Evaluation

- A. If dietary measures are unsuccessful, a secondary evaluation is undertaken.
- B. **Colonoscopy or barium enema** is necessary to rule out an organic lesion.
- C. **Assessment of Colonic Transit Time**
 - 1. **The Sitzmarks Test** consists of administering a Sitzmarks capsule containing 24 radiopaque markers. A flat-plate film of the abdomen is obtained 5 days after administration. The presence of five or more markers spread out in the colon, suggests slow transit of stool through the colon. If markers are closely clustered in the rectosigmoid segment, this indicates obstructive defecation.
 - 2. **Colonic transit scintigraphy** is a quantitative analysis of transit in the colon. The patient eats a meal laced with a radionuclide, and a gamma camera is used for 48 hours of colonic imaging.
- D. **Evaluation of Patients with Obstructive Defecation**
 - 1. **Anorectal Manometry.** A pressure probe is placed in the rectum and anus to assesses the pressure activity.
 - 2. **Defecography.** Barium is placed in the patient's rectum and the patient bears down during videofluoroscopic imaging.
 - 3. **Electromyograph.** An electrode is placed in the external anal sphincter

and myoelectrical activity is measured.

4. **Simulated Defecation.** A silicone-filled artificial stool is placed in the rectum. Difficulty in expelling the artificial stool indicates obstructive defecation.

IV. Treatment of Refractory Constipation

- A. **Saline cathartics**, such as magnesium-containing compounds and the phosphate enemas, work by an osmotic effect. Magnesium or phosphate overload may occur in renal insufficiency. Long-term use is not recommended, but may be acceptable in some circumstances. **Magnesium hydroxide** (1-2 tbsp qd-bid) is preferable. In refractory cases, a half to 1 glassful of **magnesium citrate** is effective. Rarely lactulose may be required.
- B. **Lactulose** is a hyperosmotic non-absorbable sugar that is increasingly used for the long-term management. Its advantages are nonsystemic absorption, minimal toxicity, and safety for prolonged use; 15-30 mL PO qd-bid [20 g/30 mL]. Sorbitol is significantly less expensive than lactulose; 70% solution 15-30 mL qd-bid.
- C. **Stimulant Cathartics.** Phenolphthalein is commonly found in over-the-counter preparations. Other stimulants include bisacodyl, danthron, and senna. When patients are taking these drugs chronically, they should be tapered gradually while adding fiber or sorbitol.
- D. **Emollient laxatives** (stool softeners) such as docusate increase water secretion into the colon by a surfactant effect. They may enhance the absorption of other substances, and when administered with mineral oil they can cause lipid granulomas in the lymphatic system. Docusate ([Colace] 100 mg qd-bid) is not very effective and is not recommended for long-term use.
- E. **Lubricants** (mineral oil) are not absorbed. Mineral oil can cause a severe lipid pneumonia if aspirated, and it interferes with the absorption of fat-soluble vitamins.
- F. **Lavage solutions** (CoLyte, GoLYTELY) are being used more frequently for constipation. These agents contain a balanced electrolyte solution. A gallon can be administered in 4 hours to relieve an impaction, or 8-16 oz a day can be prescribed to prevent a recurrence.
- G. **Prokinetic Agents** promote peristalsis in the colon. **Cisapride (Propulsid)** increases the frequency of bowel movements in chronically constipated patients; 10-20 mg qid; 15-30 min before meals and qhs [10 mg].
- H. **Combination therapy** with an osmotic agent combined with a lavage solution and a prokinetic agent may be used for refractory constipation.
- I. **Enemas** are a useful adjunct to laxatives, and they may sometimes be the only way to relieve severe constipation. Low-volume tap water enemas or sodium phosphate (Fleet) enemas can be given once a week to help initiate a bowel movement.
- J. **Stool Impaction.** A combination of suppositories (glycerin or bisacodyl) and enemas (phosphate) will soften the stool. Digital disimpaction may be necessary should these measures fail.
- K. **Surgery.** When the above measures are not effective, surgery may be considered as a last resort. Surgical options include colectomy and ileostomy or an ileoanal pouch.

References: See page 148.

Acute Diarrhea

I. Clinical Evaluation of Acute Diarrhea

- A. Assess the nature of onset, duration, frequency, and timing of the diarrheal episodes. Determine the stool's appearance, buoyancy, presence of blood or mucus, vomiting, and pain.
- B. Determine if contact with a potential source of infectious diarrhea has occurred.
- C. **Drugs That May Cause Diarrhea.** Laxatives, magnesium-containing compounds, sulfa-drugs, antibiotics.

II. Physical Examination

- A. **Assess Volume Status.** Dehydration is suggested by dry mucous membranes, orthostatic hypotension, tachycardia, mental status changes, and acute weight loss.
- B. **Abdominal tenderness,** mild distention, and hyperactive bowel sounds are common in acute infectious diarrhea. However, the presence of peritoneal signs or rigidity suggests toxic megacolon or perforation, requiring radiologic examination of the abdomen.
- C. **Evidence of systemic atherosclerosis** suggests ischemia. Lower extremity edema suggests malabsorption or protein loss.

III. Acute Infectious Diarrhea

- A. **Infectious diarrhea** is usually classified as noninflammatory or inflammatory, depending on whether the infectious organism has invaded the intestine.
- B. **Noninflammatory** infectious diarrhea is caused by organisms that produce a toxin (enterotoxigenic *E. coli* strains, *Vibrio cholerae*). Noninflammatory infectious diarrhea is usually self-limiting and lasts less than 3 days.
- C. **Blood or mucus** in the stool suggests inflammatory disease, usually caused by bacterial invasion of the mucosa (enteroinvasive *E. coli*, *Shigella*, *Salmonella*, *Campylobacter*). Patients usually appear to have sepsis and fever; some have abdominal rigidity and severe abdominal pain.
- D. **Vomiting out of Proportion to Diarrhea** is usually related to a neuroenterotoxin-mediated food poisoning from *Staphylococcus aureus* or *Bacillus cereus*, or from an enteric virus such as rotavirus (in an infant) or a small round virus such as Norwalk virus (in older children or adults). The incubation period for neuroenterotoxin food poisoning is less than 4 hours, while that of a viral agent is more than 8 hours.
- E. **Traveler's Diarrhea** is the most common type of acute infectious diarrhea. Typically, three or four unformed stools are passed per 24 hours, usually starting on the third day of travel and lasting 2-3 days. Accompanying symptoms may include anorexia, nausea, vomiting, abdominal cramps, abdominal bloating, and flatulence.
- F. **Antibiotic-Related Diarrhea**
 1. Diarrhea ranges from mild illness to life-threatening pseudomembranous colitis.
 2. Overgrowth of *Clostridium difficile* causes pseudomembranous colitis. Ampicillin or amoxicillin, cephalosporins, and clindamycin have been implicated most often, but almost all antibiotics can cause this complication.
 3. Patients with pseudomembranous colitis have high fever, cramping, leukocytosis, and severe, watery diarrhea.
 4. Bacterial culture for *C. difficile* requires 48 hours for results. Latex agglutination testing requires only 30 minutes.

IV. Diagnostic Approach to Acute Infectious Diarrhea

- A. Attempt to obtain a pathologic diagnosis in patients who give a history of recent ingestion of seafood (*Vibrio parahaemolyticus*), travel or camping, antibiotic use, homosexual activity, or who complain of fevers and abdominal pain.
- B. Blood or mucus in the stools indicates the presence of *Shigella*,

Salmonella, Campylobacter jejuni, enteroinvasive E. coli, C. difficile, or, less likely, Yersinia enterocolitica.

- C. Most cases of mild diarrheal disease do not require laboratory studies to determine etiology.
- D. In moderate to severe diarrhea with fever or pus in stools, a liquid stool culture for bacterial pathogens (Salmonella, Shigella, or Campylobacter) is submitted. If a history of recent antibiotic use, stools should be sent for Clostridium difficile toxin.

V. Laboratory Tests and Procedures for Acute Diarrhea

- A. **Fecal Leukocytes.** Used as a screening test in moderate to severe diarrhea. Numerous leukocytes indicate Shigella, Salmonella, and C jejuni.
- B. **Stool Cultures for Bacterial Pathogen** should be obtained if high fevers, severe or persistent (> 14 d) diarrhea, bloody stools, or leukocytes.
- C. **Examination for Ova and Parasites** is indicated for persistent diarrhea (> 14 d), travel to high-risk region, gay male, infant in day care center, or dysentery.
- D. **Blood Cultures** should be obtained prior to starting antibiotics if severe diarrhea and high fever.
- E. **E coli 0157:H7 Cultures.** Hemorrhagic E coli should be suspected if bloody stools with minimal fever, or when diarrhea follows hamburger or fast food consumption, or when hemolytic uremic syndrome is diagnosed.
- F. **Clostridium difficile Cytotoxin** is obtained if diarrhea follows use of an antimicrobial agent.
- G. **Rotavirus Antigen Test (Rotazyme).** Indicated for hospitalized children < 2 years old with gastroenteritis. The finding of rotavirus eliminates the need for antibiotics.

VI. Treatment of Acute Diarrhea

A. Fluid and Electrolyte Resuscitation

- 1. **Oral Rehydration.** For cases of mild to moderate diarrhea, administer Pedialyte or Ricelyte. For adults with travelers' diarrhea, flavored soft drinks augmented with saltine crackers is usually adequate.
- 2. **Intravenous Hydration** should be used if oral rehydration is not possible; potassium and sodium bicarbonate may be added.

B. Diet

- 1. **Infants.** Breast milk or lactose-free formula should be continued.
- 2. **Older Children and Adults:** Boiled starches (potatoes, noodles) and cereals (rice, wheat) with some salt, toast, crackers, bananas, soup and boiled vegetables. Milk products are excluded until clinically well.
- 3. Diet may return to normal when stools become formed.
- 4. The belief that only clear liquids should be ingested during diarrhea is incorrect. Clear fluids can lead to an osmotic diarrhea and electrolyte imbalance.

VII. Antimicrobial Treatment of Acute Diarrhea

A. Empiric Drug Therapy

1. Febrile Dysenteric Syndrome

- a. If diarrhea is associated with high fever and stools with mucus and blood, empiric antibacterial therapy may be given for Shigella or Campylobacter jejuni.
- b. **Children:** Trimethoprim/sulfamethoxazole and erythromycin.
Adults: Norfloxacin (Noroxin) 400 mg bid, ciprofloxacin (Cipro) 500 mg bid, ofloxacin (Floxin) 300 mg bid for 3-5 days.

2. Travelers' Diarrhea

- a. **Acute Travelers' Diarrhea.** Children with severe cases: TMP/SMX and erythromycin. Adults: Norfloxacin 400 mg bid, ciprofloxacin 500 mg bid, ofloxacin 300 mg bid for 3 days. Loperamide is added if no fever or dysentery.

- b. Persistent Travelers' Diarrhea** lasting longer than 2 weeks and nonresponsive to antibiotics is treated with metronidazole (Flagyl), 250 mg qid for 7-10 days.

B. Agent-specific Therapy

1. When culture identifies an etiologic agent in stool, specific antimicrobial therapy may be used.
2. **Shigella:** TMP/SMX DS bid PO for 3-5 d
3. **Salmonella:** Only toxic and febrile patients require antimicrobial therapy. Children, TMP/SMX for 2 weeks. Adults, ciprofloxacin 500 mg bid or ofloxacin 300 mg bid for 10 days. For milder forms of disease, antibacterials should be withheld to prevent prolongation of illness.
4. **Campylobacter jejuni:** Children: Erythromycin for 5 days. Adults: Erythromycin 250 mg PO qid for 5 days.
5. **Aeromonas, Plesiomonas, Shigelloides:** Treat as for Shigella infection.
6. **Enteropathogenic E coli:** Susceptibility testing is needed to determine optimal drug because of antimicrobial resistance.
7. **Enterohemorrhagic E coli (O157:H7):** Antibiotics are not used to treat hemorrhagic E coli colitis.
8. **Clostridium difficile colitis:** Metronidazole, 250 mg PO qid.
9. **Giardiasis:** Children: Quinacrine or furazolidone for 7 d. Adults: Quinacrine 100 mg tid or metronidazole 250 mg PO qid for 7 d.
10. **Amebiasis:** A trophozoite-active drug (metronidazole) is indicated to treat the symptoms, and a cyst-active drug (diiodohydroxyquin) is needed to prevent relapses. Adults: Metronidazole 750 mg PO tid for 5 d and diiodohydroxyquin 650 mg PO tid for 20 d.
11. **Cryptosporidiosis:** No treatment is indicated in children; adults with severe symptoms may be treated with paromomycin 500 mg PO qid for 7-10 days.

C. Symptomatic Treatment of Acute Diarrhea

1. **Attapulgite (Kaopectate):** Adults: 3 tablespoonfuls initially, repeat after each unformed stool.
2. **Antimotility Drugs**
 - a. Should not be used if fever or dysentery or for more than 48 hours.
 - b. **Diphenoxylate (Lomotil):** 1-2 tabs PO qid, max 12 tabs/day. Diphenoxylate has greater overdose liability for children; anticholinergic side effects.
 - c. **Loperamide (Imodium):** 4 mg initially, followed by 2 mg after each unformed stool, max 16 mg/d.

References: See page 148.

Chronic Diarrhea

I. Clinical Evaluation of Chronic Diarrhea

- A. Diarrhea is considered chronic if it occurs acutely, subsides, and then returns, or if it lasts longer than 2 weeks.
- B. Determine characteristics of diarrhea, including volume, mucus, blood, flatus, cramps, tenesmus, duration, frequency, effect of fasting, stress, effect of specific foods such as dairy products, wheat, laxatives, fruits. Other chronic disorders (diabetes).
- C. **Classification of Chronic Diarrhea**
 1. **Secretory** diarrhea results from increased intestinal secretion secondary to toxin production or hormonal hypersecretion (thyrotoxicosis or carcinoid).
 2. **Osmotic.** Osmotically active solutes in the gut lumen result in loss of water. Solutes include magnesium-containing laxatives, or unabsorbed carbohydrates (lactase deficiency, fructose intolerance, celiac disease, or pancreatic insufficiency).

3. **Exudative.** Mucus, blood, and proteins are discharged as a result of inflammatory bowel disease (ulcerative colitis, Crohn's disease, ischemic colitis).
 4. **Motor.** Systemic sclerosis, pseudo-obstruction, diabetes-associated neuropathic damage.
 5. **Functional.** No organic cause can be found, but psychological stress may play a role.
- D. The history can usually distinguish secretory from osmotic diarrhea.
- E. **Secretory Diarrhea**
1. Characterized by large stool volumes (>1 L per day), little or no decrease with fasting, and a fecal osmotic gap <40 .
 2. **Evaluation of Secretory Diarrhea.** Giardia antigen, Entamoeba histolytica antibody titers, Yersinia culture, fasting serum glucose, thyroid function tests, cholestyramine (Cholybar, Questran) trial.
- F. **Osmotic Diarrhea** is characterized by small stool volumes, a decrease with fasting, and a fecal osmotic gap >40 . Postprandial diarrhea with bloating or flatus also suggests osmotic diarrhea. Osmotically active laxative use may be inadvertent (sugarless gum containing sorbitol) or covert (with eating disorders).
1. **Evaluation of Osmotic Diarrhea**
 - a. Trial of lactose withdrawal
 - b. Trial of antibiotic (metronidazole) for small-bowel bacterial overgrowth
 - c. Screening for celiac disease (anti-endomysial antibody, antigliadin antibody)
 - d. Fecal fat measurement (72 hr) for pancreatic insufficiency
 - e. Trial of fructose avoidance
 - f. Stool test for phenolphthalein and magnesium if laxative abuse suspected
 - g. Hydrogen breath analysis to help identify disaccharidase deficiency or bacterial overgrowth
- G. **Exudative Diarrhea**
1. Characterized by bloody stools, tenesmus (urge to defecate), urgency, cramping pain, nocturnal occurrence. Most often due to inflammatory bowel disease, which may be indicated by the presence of anemia, hypoalbuminemia, and an increased sedimentation rate.
 2. **Evaluation of Exudative Diarrhea** is complete blood cell count, serum albumin, total protein, erythrocyte sedimentation rate, electrolyte measurement, Entamoeba histolytica antibody titers, stool culture, Clostridium difficile antigen test, ova and parasite testing; flexible sigmoidoscopy and biopsies.
- H. **Functional Diarrhea.** More common in women than men, and onset is usually before age 50. Patients usually give a long history of loose stools exacerbated by stress. Episodes are often characterized by morning urgency and relief of abdominal pain after defecation.
- I. **Small-Bowel Bacterial Overgrowth** is common in patients with decreased motility (very elderly or diabetic patients), but it can also occur in the absence of overt bowel disease.
- J. **Diabetic Diarrhea.** The presence of neuropathy or gastroparesis suggests idiopathic diabetic diarrhea. In diabetic patients, withdrawal of foods that are high in fructose or sorbitol may dramatically improve diarrhea. An antibiotic (metronidazole, tetracycline) may be tried if bacterial overgrowth is suspected.
- K. **Celiac Disease.** Antiendomysial, antigliadin, or antireticulin antibodies may be present; however, biopsy and improvement on a gluten-free diet are required for confirmation.

References: See page 148.

Neurologic Disorders

Headache

I. Clinical Evaluation of Headache

- A. Age of Onset.** Migraines frequently have an onset in childhood, adolescence, or young adulthood. An organic cause should be suspected if onset occurs later in life (temporal arteritis, cerebrovascular disease, tumor). Tension-type headaches may begin at any age.
- B. Location.** Migraine is suggested by unilateral pain that changes sides from episode to episode. Cluster headaches are strictly unilateral and orbital. Tension headaches are usually bilateral.
- C. Frequency.** Cluster headaches typically occur in brief attacks, lasting 30-90 minutes, 2-6 times a day. Migraines can also occur at sporadic intervals.
- D. Character and Severity of Headache**
 1. Subarachnoid hemorrhage causes an acute, rapid-onset, "thunderclap" headache which is often described as "the worst headache of my life."
 2. Migraine is severe, throbbing.
 3. Cluster headache pain is described as deep and boring.
 4. Tension-type headaches are dull, persistent, a band-like tightening around the head.
- E. Clinical Course.** Progressively worsening or new headaches may indicate an organic cause, such as an intracranial mass, and should be thoroughly evaluated.
- F. Prodrome and Aura.** Migraine is indicated by promontory sensations that occur before onset of headache.
- G. Precipitating Factors.** Migraine may be precipitated by bright lights, fatigue, lack of sleep, hypoglycemia, stress, alcohol, certain drugs and foods, and menstruation. Exercise or orgasm may trigger migraine or cause rupture of an aneurysm.
- H. Associated Signs and Symptoms.** Migraine commonly causes nausea and vomiting. Cluster is characterized by unilateral lacrimation and nasal congestion.
- I. Neurologic Dysfunction.** Weakness, paresthesia, aphasia, visual loss, diplopia, vertigo or loss of consciousness suggest a brain tumor or an intracranial aneurysm.

II. Physical Examination

- A.** Evaluate for hypertension, funduscopy (papilledema). Temporal artery tenderness may indicate temporal arteritis.
- B.** Tenderness in the hat-band area of the scalp and in the muscles of the neck is often a clue to tension headache.
- C. Neurologic Examination.** Cranial nerve exam (pupil and eye movement), motor strength, sensation, and meningeal irritation signs (neck stiffness) should be sought.

III. Differential Diagnosis

- A.** Life-threatening causes, such as subarachnoid hemorrhage or meningitis, are responsible for less than 1% of all headaches. If normal findings are found on general and neurologic examinations, abnormal results on CT scan are rarely present.
- B.** If the history is suggestive of intracranial bleeding CT scan without contrast should be performed. If the CT scan is normal, a lumbar puncture is mandatory to rule out intracranial bleeding.
- C. Indications for CT or MRI Scan**
 1. An isolated, severe headache
 2. Consistently localized head pain
 3. Pain severe enough to disturb sleep

58 Headache

4. Abrupt onset, or onset during physical exertion (leaking aneurysm, elevated intracranial pressure, or arterial dissection)
5. Progressively worsening headaches
6. Abnormal neurologic findings, neck stiffness, or fever
7. The patient appears acutely ill and is confused or drowsy

IV. Non-Pharmacologic Therapy of Migraine Headache

- A. Avoiding known triggers, such as caffeine or too little sleep, and stress reduction, local pressure, heat, or ice packs may ease the pain.
- B. Patients with migraine (especially menstrual migraine) may improve after discontinuation of oral contraceptives.

V. Abortive Drug Treatment for Migraine Headaches

- A. **Abortive Therapy** is aimed at stopping individual attacks after they have begun. Treatment is initiated at the first sign of headache.

Abortive Drug Treatment of Migraine Headaches

Drug	Regimen
Nonsteroidal Anti-inflammatory Drugs Ibuprofen (Motrin)	400-600 mg at onset, then 300-800 mg PO qid [200, 300, 400, 600, 800 mg].
Naproxen sodium (Aleve)	825 mg followed 30 min later by 275-550 mg q4-6h prn, max 1375 mg/d [275, 550 mg].
Ketorolac (Toradol)	30 or 60 mg IM initially followed by 30 mg every 6 hours as needed; or 10 mg PO q4-6h prn [10 mg].
Ketoprofen (Orudis)	50-75 mg PO tid [25, 50, 75 mg].
Mefenamic acid (Ponstel)	200-500 mg at onset then 250 mg PO qid [250 mg].
Combination Midrin (isometheptene mucate/dichloralphenazone/acetaminophen).	2 capsules at headache onset, then take 1 q1h until relief; max 5 capsules in 12h.
Esgic, Fiorinal (aspirin, caffeine, butalbital)	1-2 tablets or capsules with onset of attack, then q4h; max 6 per attack.
Fioricet (acetaminophen, caffeine, butalbital)	1-2 tablets or capsules with onset of attack, then q4h; max 6 per attack.
Fiorinal w/codeine (aspirin, caffeine, butalbital, codeine)	1-2 capsules with onset of attack, then q4h; max 6 per attack.
Ergot Preparations Cafergot, Wigraine tablets (ergotamine/caffeine)	2 tablets at onset, then one q30min, max 6 per attack. Use for no more than 2 attacks/wk. Max: 10 tablets/wk.
Wigraine suppositories (ergotamine/caffeine)	1 suppository at onset; may repeat once in 1 h; max 2 attacks/wk, 2 suppositories per attack.

Dihydroergotamine (DHE 45)	1 mg SC q8-12h
Narcotic Analgesics Butorphanol nasal spray (Stadol NS)	1 spray (1 mg) in one nostril at onset of headache; may repeat in 4 h prn.
Serotonin Agonist Sumatriptan injection (Imitrex)	6 mg SC, max two injections in 24h; or 25-100 mg PO with fluids, repeat q2h prn, max 300 mg/d PO; or 6 mg SC and 200 mg PO in 24h [25, 50 mg tabs]

B. Sumatriptan (Imitrex)

1. In the emergency department, sumatriptan injection (Imitrex), the only specific agonist to serotonin (5-HT) receptors on intracranial vascular nerves, is the drug of choice. It is effective in 70-80% of patients. Sumatriptan has minimal side effects compared to ergotamine and dihydroergotamine which cause significant nausea and vasoconstriction.
2. **Oral Dose.** 25-100 mg PO with fluids, repeat q2h prn, max 300 mg/d PO; or start with 6 mg by subcutaneous injection, followed by 200 mg PO in 24h [25, 50 mg tabs]; contraindicated in ischemic heart disease, pregnancy, or concurrently with ergotamines.

C. Dihydroergotamine

1. Dihydroergotamine injection (DHE 45), a 5-HT receptor agonist, is highly effective in the emergency management of migraine. Relief occurs in 15-30 minutes following IM administration and persists for 3-4 hours. 1 mg IV over 2-3 minutes with metoclopramide (Reglan), 10 mg mixed with 50 mL of 5% dextrose in water and given IV over 30 min IV q8h for 48 hours.
2. Discharge the patient with DHE to self-administer SC, 1 mg q8-12h, and propranolol HCL (Inderal), 40-80 mg po tid.
3. Contraindicated in ischemic heart disease and pregnancy.

D. Ergotamine Combinations (Wigraine, Cafergot)

1. Effective for treatment of migraine not relieved by simple analgesics, but often associated with rebound headaches; may cause peripheral vascular insufficiency and angina.
2. **Contraindications.** Coronary artery disease, peripheral vascular disease, hypertension, renal and hepatic disease, pregnancy.
3. **Side Effects.** Nausea, vomiting, paresthesias; chest discomfort is a cause for concern.

E. Narcotic Therapy

1. Codeine combination analgesics such as Vicodin may occasionally be indicated for infrequent, severe attacks. When taken more than three times a week, codeine may cause rebound headache.
2. Butorphanol (Stadol) 1 spray in one nostril, may repeat in 60-90 minutes if needed. Repeat 1 dose sequence q3-4h prn [2.5 mL bottle].

VI. Prophylactic Therapy for Migraine Headaches

- A. Prophylactic medications prevent headache from occurring, and should be used when attacks are more frequent than 2-3 per month or if attacks are severe.

Prophylactic Therapy of Migraine Headaches

Drug	Regimen
Valproic acid (Depakote)	250 mg bid for 3 days, then 500 mg bid
Beta-Blockers Propranolol (Inderal) Propranolol LA (Inderal LA) Atenolol (Tenormin) Metoprolol (Lopressor)	40-80 mg PO bid-tid [40, 60, 80 mg] 80-160 mg PO qd [80, 120, 160 mg] 50-100 mg PO qd [25, 50, 100 mg] 100 mg qd
Tricyclic Antidepressants Amitriptyline (Elavil) Desipramine (Norpramin) Nortriptyline (Pamelor)	25-50 mg qhs 25-50 mg qd in AM 25-50 mg qhs

- B. **Valproic Acid (Depakote)** is highly effective for prophylactic therapy. Liver dysfunction and weight gain may occur.
- C. **Beta Blockers.** Propranolol reduces the frequency of migraine in 51%. Contraindications include congestive heart failure, diabetes, asthma. Side effects include depression, decreased exercise intolerance.
- D. Amitriptyline (Elavil) effectively reduces the frequency and severity of migraine.

References: See page 148.

Vertigo

I. Differentiation of Central Causes of Vertigo from Peripheral Causes

- A. Vertigo is a sensation of abnormal motion either of the surroundings or of the body; vertigo may be described as spinning, whirling, swaying, or "the room is moving."
- B. 85% of patients with vertigo have a peripheral vestibular disorder, 15% have a central nervous system disorder.
- C. Peripheral disorders may have associated hearing loss and tinnitus, without other neurologic deficits. Vertigo from peripheral lesions often develops acutely and is intermittent and shorter-lasting; peripheral lesions tend to cause more severe vertigo, with associated nausea and vomiting.
- D. Central lesions, such as cerebral tumors, are not associated with hearing loss, but may be accompanied by other neurologic signs reflecting brain-stem involvement. Symptoms of central lesions develop more insidiously and are longer-lasting and more continuous (except for vascular events); central lesions usually cause less severe vertigo and nausea.

II. Peripheral Causes of Vertigo

A. Benign Positional Vertigo

1. Most common single cause of vertigo, occurring twice as frequently as any other vestibular disorder. Intense but brief episodes of vertigo are associated with changes in head position, usually when lying down. Resolves within 3-6 months, but may recur.
2. **Neurologic Examination:** Normal, except for positional nystagmus (induced by rapid head movement).
3. **Etiology.** May occur after trauma or viral infections; majority are idiopathic. Average age 51 years; increased incidence with advancing age. The mechanism may be sediment falling on the cupula of the semicircular canal.
4. **Hallpike Maneuver** confirms the diagnosis of BPV. The patient's head is rotated to one side and then gradually lowered to 30° below the horizontal position. When the affected ear is in the downward position.

nystagmus and vertigo is triggered after a few seconds. Vertigo fades within 30 seconds; nystagmus is usually rotatory and changes direction when the patient sits up.

B. Vestibular Neuronitis

1. Sudden severe vertigo, lasting up to 10 days. Nausea and vomiting are common; no hearing loss or neurologic signs. Typically follows a viral upper respiratory infection.
2. Residual unsteadiness may persist for several weeks after an attack.

C. Meniere's Disease

1. Episodic vertigo, tinnitus, fullness in the ear, progressive sensorineural hearing loss; usually unilateral.
2. Severe vertigo develops rapidly over a few minutes, and lasts for several hours. It is caused by an abnormal accumulation of endolymphatic fluid in the inner ear.

D. Motion Sickness

1. Nausea, dizziness, abdominal distress, increased salivation, and vomiting provoked by motion.
2. Can be reduced by visually fixing eyes at the horizon.

E. Tumors of Cerebello-pontine (CP) Angle

1. Acoustic neuroma or metastases of tumor to cerebellopontine angle.
2. Vertigo, deafness, nystagmus, ataxia; facial weakness, disturbance in taste.

F. Other Disorders Associated with Vertigo

1. Impacted cerumen or foreign bodies in the external auditory canal; otitis media, cholesteatoma, otosclerosis, mastoiditis, local ear trauma, and perilymphatic fistula.
2. Ototoxic drugs: Aminoglycosides, loop diuretics, aspirin, quinine, caffeine, alcohol, phenytoin.

III. Central Causes of Vertigo

A. Diseases affecting the brain stem and cerebellum may cause central vertigo; vertigo is usually not the dominant manifestation of these disorders.

B. Toxic. Various medications/drugs, alcohol, narcotics, analgesics; dilantin nystagmus with excessive levels over 30

C. Drug interactions. Darvon plus Tegretol--increased level of Tegretol

D. Volatile hydrocarbons, solvents

E. Vascular. Brain stem infarction--Wallenberg syndrome--lateral medullary syndrome

1. Ipsilateral ataxia, Horner's syndrome, palatal paralysis, loss of pain and temperature, nystagmus.

2. Contralateral loss of pain and temperature in extremities and trunk

F. Tumors. Cerebellar and other

G. Infectious. Brain stem encephalitis, basilar meningitis

H. Traumatic. Basilar skull fracture; brain stem/cerebellar contusion

I. Other. Multiple sclerosis and other demyelinating diseases

IV. Presyncope

A. Dizziness is associated with the feeling of an impending faint; no loss of consciousness; caused by a transient reduction in cerebral blood flow due to inadequate cardiac output, orthostatic hypotension, or noncardiac causes.

B. Vaso-vagal Reflex Presyncope. A common cause of presyncope occurring after stressful, painful, or other noxious stimuli leads to peripheral vasodilatation with a drop in heart rate and cardiac output.

C. Orthostatic Hypotension

1. Measurement of systolic blood pressure reveals a 20 mmHg or more BP drop within 3 minutes of assuming an upright posture.
2. **Factors Causing Orthostatic Hypotension.** Decreased intravascular volume from hemorrhage, dehydration, diarrhea, vomiting, or diuresis; antihypertensives, nitrates, phenothiazines, antidepressants, prolonged bedrest. Primary autonomic insufficiency due to diabetic multiple

62 Vertigo

autonomic system atrophy (Shy-Drager's syndrome) is less common.

- D. Arrhythmias.** Bradycardia <40 beats per minute or tachyarrhythmias are a significant cause of dizziness and presyncope.
- E. Other Cardiac Causes of Presyncope.** Aortic stenosis, hypertrophic cardiomyopathy, ischemia, constrictive pericarditis, cardiac tamponade, carotid sinus hypersensitivity.
- F. Metabolic Causes of Presyncope.** Hypoglycemia and hypoxemia are rare causes of dizziness. True hypoglycemia is rare in nondiabetics and is usually a complication of insulin and oral hypoglycemics.

V. Lightheadedness

- A.** Lightheadedness is described by the patient as a vague "giddy" or "woozy" sensation.
- B.** Anxiety disorder is commonly associated with lightheadedness secondary to hyperventilation, and reproduction of symptoms occurs with hyperventilation.

VI. Clinical Evaluation of the Dizzy Patient

- A. Categorize the Form of Dizziness.** Differentiate vertigo (spinning or moving) from a nonvertiginous sensation (giddiness, unsteadiness, faintness).
- B.** Determine the onset and duration of the episodes, provoking factors, head position; associated nausea and vomiting, hearing loss or tinnitus.
- C. Differentiate Central Causes from Peripheral Causes**
 - 1. Central Causes** are indicated by neurological signs, dysphagia, diplopia, dysarthria, or hemiparesis. Ataxia may suggest cerebellar disease.
 - 2. Perform a Careful Neurologic Examination**
 - 3.** Ear, nose, throat exam should be done to rule out impacted cerumen, middle-ear disease, hearing loss.
 - 4.** A history of hearing loss or tinnitus localizes the problem to the ear or the eighth nerve.
- D. Additional Testing.** Electrolytes, glucose, complete blood count. Audiologic evaluation and electronystagmography may be indicated.
- E. If there are no neurologic abnormalities, hearing loss, or an ear abnormalities,** the most likely causes are BPV and vestibular neuronitis. The Hallpike test can establish the diagnosis of BPV. Assess blood pressure to exclude orthostatic hypotension.
- F. If the neurologic examination shows abnormal cranial nerve or cerebellar findings,** an MRI should be used to rule out acoustic neuroma, tumor, or infarction.

VII. Management of Vertigo

- A. Treatment of Acute Vertigo**
 - 1.** Stop vomiting with prochlorperazine (Compazine) suppository, 25 mg q4-6h prn
 - 2.** Diazepam (Valium) 2 mg tid
 - 3.** Meclizine (Antivert) 25-50 mg PO q6h prn [12.5, 25, 50 mg].
 - 4.** Sodium restriction 4 gm or less daily
 - 5.** Correct sensory deficits if possible
- B. Benign Positional Vertigo.** Deliberate repetition of the head maneuvers that elicit the symptoms of vertigo may lessen the severity and duration.
- C. Vestibular Neuronitis.** Managed with bedrest and meclizine (Antivert) 25-50 mg PO q6h; diuretics and salt restriction.
- D. Lightheadedness.** Treat anxiety, depression, or panic attacks with anxiolytics or antidepressants. Hyperventilation is treated by deliberate slow breathing.
- E. Meniere's Disease.** Acute attacks are managed with meclizine and bed rest. For refractory cases, ablative surgery of the vestibular nerve or labyrinthectomy may relieve symptoms but sacrifice hearing on involved side.

References: See page 148.

Epilepsy

I. Classification of Seizures

- A. Seizures are classified into two broad categories, partial or generalized.
- B. **Partial seizures** are characterized by focal signs and symptoms that depend on the focus of the seizure.
 1. Partial seizures produce either motor activity restricted to focal regions of the body (simple partial) or behavioral changes (complex partial).
 2. **Simple partial seizures** are characterized by involuntary focal motor movements or abnormal sensations without any alteration in consciousness.
 3. **Complex Partial Seizures** are characterized by a change in consciousness during the seizure, and are the most common form of seizures. Patients frequently experience postictal confusion, fatigue, and impaired or absent memory of the event. Complex partial seizures often secondarily generalize, culminating in a tonic-clonic seizure.
 4. **Secondarily Generalized Partial Seizures** occur when a partial seizure becomes generalized.
- C. **Generalized Seizures**
 1. Generalized tonic-clonic seizures are characterized by an abrupt loss of consciousness and tonic extension of the extremities, followed by generalized clonic movements. The typical generalized seizure lasts less than 2 minutes and is followed by a 5- to 10-minute postictal period of diminished responsiveness.
 2. Absence seizures are nonconvulsive and are characterized by abrupt cessation of activity and a blank stare. The duration is generally less than 20 seconds.

II. Clinical Evaluation of the Seizure Patient

- A. **Characteristics of Seizure.** A complete description of the attack should be obtained from a witness, including tonic-clonic movements, tongue biting, or incontinence.
- B. **Prodrome** symptoms occur hours or minutes before a seizure, and they include any warning or premonition of seizure, such as a dull headache, abdominal discomfort, fear, or unusual movements.
- C. **Aura** consists of emotional or experiential phenomenon perceived during the initial moments of a seizure.
- D. **Seizure Beginning.** Seizures often begin with a motionless stare or extension of the arms (tonic activity). Convulsive motor movements occur later in the episode (clonic activity).
- E. **Precipitating Events** include noncompliance with medications, photic stimulation, emotional stress, fatigue, and sleep deprivation.
- F. In adults, illicit drug abuse and human immunodeficiency virus infection are becoming increasingly frequent causes of seizures. In older adults, cerebrovascular disease or metastatic malignancy may cause seizures. In patients older than 60 years, seizures are caused by stroke in approximately one third of cases.

III. Physical Examination

- A. Signs of injury should be sought. Oral examination may reveal tongue lacerations or broken teeth. Extremity exam may reveal contusions. Evidence of incontinence may be apparent.
- B. **Neurologic Examination** may reveal focal neurologic abnormalities.
- C. Almost any central nervous system (CNS) insult and many systemic disorders can produce convulsions.

Common Causes of Generalized Seizures

Noncompliance with anticonvulsant medications Cerebrovascular accident Central nervous system infection Intracranial neoplasm (primary, meta-static) Head trauma Alcohol abuse (intoxication, withdrawal) Drug overdose (cocaine, amphet-amines, cyclic antidepressants, theophylline, isoniazid)	Metabolic disorders (hypoglycemia, hyponatremia, hypocalcemia, hypoxia, acidosis, hyperosmolar states, uremia) Eclampsia Febrile illness Idiopathic
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IV. Laboratory Testing

- A. Electroencephalography.** A routine study should include photic stimulation, hyperventilation, sleep deprivation, and awake and asleep tracings.
- B. Magnetic Resonance Imaging (MRI)** has a higher diagnostic yield than CT scan.
- C. Serum anticonvulsant levels** should be measured if the patient has an established seizure disorder.
- D. Initial Laboratory Evaluation for First-Time Seizure.** Serum electrolytes, glucose, calcium, magnesium, BUN, creatinine; complete blood count, liver enzymes, toxicology screen, urinalysis, arterial blood gases.
- E. Lumbar Puncture** is unnecessary unless there is a specific reason to analyze cerebrospinal fluid.

V. Pharmacotherapy of Epileptic Seizures

- A.** Therapy is initiated with a single antiepileptic drug at a low dose, which is slowly increased until the serum level is in therapeutic range.
- B. Dosing Schedule.** Drug steady state is not reached until 4-5 half-lives have elapsed. A loading dose is usually not necessary.
- C.** Serum levels above the suggested therapeutic range may be necessary in some patients. Trough concentrations should be measured, preferably from serum samples drawn before the morning dose is taken.
- D.** If the initial agent fails to control seizures, a second drug is substituted. Drug combinations should be tried only if monotherapy fails.

Drug Choices for the Treatment of Epileptic Seizures

Seizure Type	First-Line Therapy	Alternative Therapy
Generalized tonic-clonic	Carbamazepine Valproic acid (Depakote) Phenytoin (Dilantin)	Phenobarbital Felbamate (Felbatol) Gabapentin (Neurontin) Lamotrigine (Lamictal)
Partial (both simple and complex)	Carbamazepine Valproic acid Phenytoin	Phenobarbital Felbamate Gabapentin Lamotrigine

Pharmacologic Properties of Antiepileptic Drugs

Drug	Starting Dose	Maintenance Dose	Dosage	Therapeutic Level
Carbamazepine (Tegretol)	6 mg/kg/day (200 mg bid)	5-20 mg/kg/day (200-400 mg bid-tid)	2-3 times daily	4-12 mcg per mL

Phenytoin (Dilantin)	4-6 mg/kg/day (300 or 200 mg bid)	Same	1-2 times daily	10-20 mcg per mL
Valproic acid (Depakote)	10-15 mg per kg/day (250 mg tid-qid)	15-60 mg/kg/day (500-1000 mg tid-qid)	2-4 times daily	50-100 mcg per mL
Phenobarbital	1-3 mg/kg/day (60-100 mg qd-bid)	Same	1-2 times daily	10-30 mcg per mL
Ethosuximide (Zarontin)	10 mg/kg/day (250 mg bid)	10-20 mg/kg/day (500-750 mg bid)	2 times daily	50-100 mcg per mL
Felbamate (Felbatol)	1,200 mg per day (400 mg tid)	3,600 mg per day (400-600 mg tid-qid)	3 times daily	N/A
Gabapentin (Neurontin)	1,200 mg per day (300 mg tid)	3,600 mg per day (400-600 mg tid)	3 times daily	N/A
Lamotrigine (Lamictal)	50-100 mg bid	100-250 mg bid	2-3 times daily	N/A

E. Carbamazepine

1. Lacks cognitive and behavioral side effects. Carbamazepine has antiepileptic activity against partial and generalized seizures.
2. Dizziness, diplopia, agitation, and transient, benign leukopenia are common. Infrequently, a syndrome of inappropriate antidiuretic hormone secretion may occur. Aplastic anemia has been rarely reported.

F. Phenytoin

1. Antiepileptic activity is comparable to that of carbamazepine.
2. Therapeutic level phenytoin is 10-20 mcg/mL.
3. **Dose-related Adverse Effects.** Nausea, vomiting, nystagmus, and ataxia, gingival hyperplasia (20%), hirsutism, acneiform eruptions, and coarsening of facial features.

G. Valproic Acid

1. Valproic acid (Depakote) has the widest spectrum of activity, with efficacy against partial, generalized tonic-clonic and absence seizures.
2. Initial dosage 10-15 mg/kg, increasing at one- to two-week intervals, to a maximum of 60 mg/kg/day.
3. Gastrointestinal symptoms and drowsiness occur at the onset of therapy. Tremor, thrombocytopenia, weight gain may occur. Rarely, fatal hepatotoxicity occurs.

H. Felbamate (Felbatol)

1. Adjunctive therapy for partial seizures in adults.
2. Broad spectrum of activity, similar to that of valproic acid. It has a wide therapeutic index.
3. **Adverse Effects:** Mild neurotoxicity, nausea and vomiting, insomnia and anorexia. Aplastic anemia rarely.

I. Gabapentin (Neurontin)

1. Drug interactions are highly unlikely because it is not protein-bound,

not metabolized, and does not induce liver enzymes.

2. Adjunctive therapy for partial seizures.

J. **Lamotrigine (Lamictal)** has demonstrated efficacy comparable to the other new agents, primarily in patients with partial seizures.

K. **Indications for Surgical Treatment of Epilepsy.** Seizures continuing after a drug therapy may be amenable to surgical removal of the seizure focus.

References: See page 148.

Dementia and Alzheimer's Disease

I. Classification of Neurologic Syndromes

A. **Dementia** is characterized by a decline from a previous higher level of intellectual function of sufficient severity to interfere with social or occupational performance or both. Dementia is a syndrome produced by many disorders including Alzheimer's disease.

B. **Delirium** is a disorder of attention (abnormal consciousness), characterized by lethargy, stupor, or coma.

C. **Pseudodementia** is depression that mimics dementia. Ten percent of patients presenting with symptoms of dementia actually have primary depression.

1. Dementia presents with a more global decline in cognitive function than does depression.
2. Patients with dementia often attempt to disguise their cognitive deficits with confabulation. Dementia patients usually make a real effort to answer correctly. Social skills are preserved in dementia.
3. Patients with primary depression often show diminished effort, and responses are characterized by low self esteem. Depression may be associated with decreased appetite, weight loss, decreased energy, crying spells, anhedonia, and hypersomnia or insomnia.

II. Causes of Dementia

A. **Alzheimer's Disease** is the most frequent cause of dementia; it accounts for 50-80% of subjects with dementia. It has an insidious onset with gradual progression over years

1. Early difficulty with memory, then anomia, then more widespread cognitive impairment and behavioral alterations are characteristic. Mental status changes, aphasia, memory loss, visuospatial deficits, indifference, and delusions occur; motor function remains intact.
2. The neurologic exam is usually normal.
3. **Neuroimaging.** CT and MRI may be normal or show atrophy.
4. **Diagnostic Criteria for Alzheimer's Disease**
 - a. Presence of dementia as established by clinical examination and mental status testing.
 - b. Deficits in two or more areas of cognition (affect, executive function, language, praxis, visual spatial relations, calculation, judgement orientation).
 - c. Progressive worsening of memory and cognition.
 - d. Medical evaluation has excluded systemic disorders or other brain diseases that could cause cognitive deficits.

B. Other Causes of Dementia

1. Frontal Lobe Degenerations
2. Vascular Dementia (multi-infarct dementia)
3. Normal pressure hydrocephalus
4. Jakob-Creutzfeldt disease
5. AIDS dementia complex (HIV encephalopathy)
6. CNS infections (neurosyphilis)
7. Thyroid dysfunction, B12 deficiency

8. Hepatic encephalopathy, alcohol-related dementia
9. Iatrogenic (antihypertensives, psychotropics, anticonvulsants)

III. Evaluation of the Dementia Patient

- A. Assess the tempo of cognitive decline, the characteristics of deficits, family history, and exclude reversible causes of dementia.
- B. **Mental Status Testing.** Orientation, recent and remote memory, language, praxis, visuospatial relations, calculations, and judgment are tested.
- C. **Neurologic Examination** is usually normal in Alzheimer's disease. Focal abnormalities, extrapyramidal signs, movement disorders, and abnormalities of gait should be sought to exclude other causes of dementia.
- D. **Neuropsychological Testing** supports the diagnosis of dementia and is useful for follow-up evaluation; however, testing is not necessary to diagnosis Alzheimer's disease.

Laboratory Evaluation of Patients with Dementia

Routine	When Indicated
CBC, ESR Chemistry panel Liver function panel Syphilis serology TSH B12 level EKG CT with and without contrast is adequate for exclusion of structural disorders. MRI is better for detecting ischemia	CSF examination EEG Neuropsychological testing HIV testing

IV. Treatment of Alzheimer's Disease

- A. The **cholinergic hypothesis** proposes that the cognitive deficits of Alzheimer's disease are caused by declining function of acetylcholine-mediated neuronal systems.
- B. Anti-Alzheimer's disease drugs are centrally acting cholinesterase inhibitors that increases levels of acetylcholine within synapses.
- C. **Donepezil (Aricept)**
 1. Donepezil is an effective treatment for mild-to-moderate Alzheimer's disease and it is better tolerated than tacrine. It improves cognitive function or delays progression of disease in 82%.
 2. 5 mg PO qhs x 4-6 weeks, then 10 mg qhs [5, 10 mg]; may cause mild and transient nausea, diarrhea, vomiting, muscle cramps, and anorexia.
 3. Unlike tacrine, donepezil rarely causes hepatotoxicity; increased transaminase levels occur in <1%. Unlike tacrine, donepezil does not interact with theophylline, cimetidine, or warfarin.
- D. **Tacrine (Cognex)**
 1. **Efficacy.** A small benefit occurs in patients' scores on functional ratings, and caregivers subjectively report less decline in overall status.
 2. Tacrine is only indicated for patients with mild to moderate Alzheimer's disease who are otherwise healthy.
 3. Tacrine may increase theophylline concentrations two-fold. Tacrine plasma levels are significantly increased by cimetidine.
 4. **Contraindications.** Asthma, atrioventricular conduction defects, hyperthyroidism, urinary tract obstruction, peptic ulcer disease. Caution in seizure disorders, closed angle glaucoma, or history of

liver disease.

5. Starting dosage 10 mg four times daily, given between meals on an empty stomach. Daily dosage may be increased at six-week intervals by increments of 40 mg per day if a clinical response is not initially observed. [10, 20, 30, and 40 mg capsules].
6. Most patients who respond will require a dosage of at least 80 mg per day, but sustained benefit may be more likely at dosages of 120-160 mg per day.
7. Hepatotoxicity is the most common and most significant side effect. ALT levels should be monitored weekly for at least the first 18 weeks of treatment and repeated every 3 months thereafter if values remain in the normal range. Nausea, vomiting, diarrhea, anorexia, and abdominal pain occur in 9-35%.

References: See page 148.

Endocrinologic, Renal, and Orthopedic Disorders

Hyperlipidemia

I. Clinical Evaluation of Hyperlipidemia

- A. Screening for hyperlipidemia should begin in men 35 years of age and over, and in women 45 and older or after menopause. Screening should be repeated every 5 years and is continued until age 75.
- B. Screening usually consists of a fasting LDL-cholesterol and HDL-cholesterol.
- C. **LDL-cholesterol is calculated as follows:**

$$\text{LDL cholesterol} = \text{total cholesterol} - \text{HDL cholesterol} - (\text{triglyceride}/5)$$
- D. **Treatment of hyperlipidemia relies upon CHD risk to guide therapy**
 1. Patients with CHD or other atherosclerotic disease are at the highest risk, and the target levels of LDL-cholesterol are lower in such patients.
 2. Age is a major CHD risk factor (>45 in men and ≥55 in women).
 3. The targets for drug therapy in low risk young men and premenopausal women are higher (LDL >220 mg/dL).
 4. High HDL-cholesterol (≥60 mg/dL) is a negative risk factor, and HDL level is considered in selection of medications.
- E. Elderly patients with evidence of CHD should be screened and treated for high blood cholesterol in a manner similar to other high risk adults. However, elderly adults without evidence of CHD or atherosclerosis do not need screening for high blood cholesterol or cholesterol-modifying therapy.
- F. **Role of HDL-cholesterol**
 1. Low HDL (<35 mg/dL) is considered an independent risk factor for CHD. However, there is no evidence that using drugs to raise an isolated low HDL with a normal LDL-cholesterol offers any benefit.
 2. HDL-cholesterol level is an important factor in drug selection. Niacin has a significant positive effect on HDL. Bile acid sequestrants have only a minimal effect on HDL, and statins have an intermediate effect on HDL-cholesterol.
 3. Estrogen has a HDL raising effect and LDL-lowering effect. Hormone replacement therapy should be considered in all menopausal women with lipid disorders.
 4. Despite its HDL raising effect, less emphasis is currently placed on gemfibrozil because of its modest effect on LDL-cholesterol and particular concerns about fibric acid derivatives and non-CHD mortality. There is little role for probucol as a lipid-modifying drug due to its marked HDL-lowering effects.

II. Clinical Management of High LDL-Cholesterol

- A. Different levels of aggressiveness of therapy are based on the assessment of CHD risk.
- B. **Risk Factors for Coronary Heart Disease**
 1. **Positive Risk Factors**
 - a. **Age:** Male: age >45. Women: >55 or menopause before age 55 without estrogen replacement therapy.
 - b. **Family History of Premature Coronary Heart Disease:** Father or brother with coronary heart disease before age 55; mother or sister before age 65.
 - c. **Cigarette Smoking**
 - d. **Hypertension:** >140/90 mm Hg or currently taking antihypertensive medication
 - e. **Low HDL-cholesterol level:** <35 mg/dL

70 Hyperlipidemia

f. Diabetes mellitus

2. Negative Risk Factor

- a. **High HDL** >60 mg/dL, subtract one risk factor from the total.

C. Three risk groups

1. **Low Risk:** <2 risk factors.
2. **Intermediate Risk:** >2 risk factors.
3. **High Risk:** CHD or other atherosclerotic disease.

Diet and Drug Treatment Based on LDL-Cholesterol

Category	Diet	Drug	Goal LDL
Coronary Heart Disease	>100 mg/dL	>130 mg/dL	<100 mg/dL
>2 Risk Factors	>130 mg/dL	>160 mg/dL	<130 mg/dL
<2 Risk Factors	>160 mg/dL	>190 mg/dL	<160 mg/dL
Young (men <35 and premenopausal women)	>160 mg/dL	>220 mg/dL	<160 mg/dL

III. Treatment of Hypercholesterolemia

- A. Dietary therapy and physical activity** modification consist of reduced intake of saturated fats and cholesterol, and weight loss in overweight patients.
- B.** Bile acid sequestrants, niacin, and the HMG-CoA reductase inhibitors (lovastatin, pravastatin, simvastatin and fluvastatin) are the major drugs used to treat hyperlipidemia. The sequestrants should be avoided because of their considerable expense, poor side effect profile, and limited effect on HDL-cholesterol.
- C.** Estrogen replacement therapy is important in post-menopausal women.
- D.** Psyllium is also an effective adjunct to diet and/or drug therapy for reducing LDL-cholesterol.

Lipid-Modifying Effects of Cholesterol-Lowering Medications

Drug	LDL-cholesterol	HDL-cholesterol
Niacin	↓15-25%	↑25-35%
Bile Acid Sequestrants (resins)	↓15-25%	↑5%
Statins	↓20-40%	↑10%
Estrogen	↓15%	↑15%
Psyllium	↓10-15%	0%

Patient Selection for Medications of First Choice

Indication	Recommended Drugs
Primary Prevention Pre-menopausal Women (rarely necessary)	Niacin, Bile acid sequestrants, ? Statin
Primary Prevention Men (35-75)	Niacin, Bile acid sequestrants, Statin
Primary Prevention Post Menopausal Women (50-75 yrs)	Estrogen, Niacin, ? Statin
Secondary Prevention Men	Statin, Niacin, Combinations
Secondary Prevention Women	Estrogen, Statin, Niacin, Combinations

E. Niacin (Nicotinic Acid)

1. Reduces LDL 15-25%, raises HDL 25-35%.
2. Niacin is highly effective because it exerts beneficial effects on both LDL and HDL. It is inexpensive, but side effects are common. It is valuable in treating high blood cholesterol with low HDL-cholesterol levels.
3. Niacin should be initiated at low doses (eg, 100 mg with dinner). First week: 100 mg/day; 2nd week: 200 mg/day; 3rd week: 400 mg/day; 4th week: 800 mg/day; 5th week: 1500 mg/day. At 1.5 grams per day, blood HDL-cholesterol response should be reevaluated. If response is inadequate, the dosage is advanced to 3.0 gm (1.5 gm bid) as tolerated [100, 250, 500 mg].
4. Flushing will be significantly reduced with aspirin 81-325 mg/day, 30 minutes before dose.
5. **Side Effects:** Cutaneous flushing, nausea, abdominal discomfort, skin dryness. Hepatitis, hyperglycemia, hyperuricemia, gout, and peptic ulcer disease may occur.
6. **Contraindications:** Gout or hyperuricemia, liver disease, peptic ulcer disease, diabetes.
7. Periodic monitoring of aminotransferases and alkaline phosphatase is necessary.
8. Slow-release forms are not recommended because of decreased efficacy and increased hepatic toxicity.

F. Bile Acid Sequestrants (Resins)

1. The bile acid sequestrants, **cholestyramine (Questran)** and **colestipol (Colestid)**, bind intestinal bile acids.
2. The agents can lower LDL by 15-25%; minimal increase in HDL (5%).
3. **Dosage:** Start with 1 packet or scoop bid before, during, or after meals; increase up to 3 packets or scoops bid.
4. **Common Side Effects:** Constipation, diarrhea, nausea, flatulence, abdominal pain. Constipation may be prevented by increasing dietary fiber and using stool softeners.
5. Bile acid sequestrants bind anionic drugs (warfarin, thyroxine, digoxin, thiazides, beta blockers, statins). These agents should be taken 1 hour before or 4 hours after resin dose.

G. Statins (HMG-CoA Reductase Inhibitors)

1. Statins are the most effective and most potent drugs available for reducing LDL cholesterol. They are useful for severe hypercholesterolemia and maximal lowering of LDL levels (eg, 40%).
2. More effective than niacin in lowering LDL but less so for raising HDL. Reduces LDL cholesterol by 20-40%. HDL cholesterol increases by only 5-15%. Statins have a low incidence of side effects. These agents interfere with hepatic cholesterol synthesis.

72 Type I Diabetes Mellitus

3. Dosages

- a. Simvastatin (Zocor) 10 mg qhs with meals; max 40 mg /d [5, 10, 20, 40 mg tabs]; most cost effective agent.
- b. Fluvastatin (Lescol) 20-40 mg qhs at bedtime, max 80 mg/d [20, 40 mg].
- c. Lovastatin (Mevacor) 20-40 mg qhs-bid with meals; max 80 mg/day [10, 20, 40 mg].
- d. Pravastatin (Pravachol) 20 mg qhs with meals; max 40 mg /d [10, 20, 40 mg].
- e. Atorvastatin (Lipitor) 10 mg qd initially, then increase up to 80 mg/day [10, 20, 40 mg]

4. **Side Effects:** Well tolerated; significant side effects are uncommon. Nausea, fatigue, insomnia, myalgias, headaches; changes in bowel function, skin rashes. Less commonly myopathy and elevations in liver enzymes. Contraindicated in hepatic disease.

5. **Liver Function Tests** should be checked if the patient develops signs of hepatitis.

IV. Monitoring of Drug Therapy

- A. After starting drug therapy, LDL-cholesterol level should be measured in 4-6 weeks, and then again in 3 months.
- B. Drug therapy is usually continued for many years or for life.
- C. If the response to initial drug therapy is not adequate, then switch to another drug, or to a combination of two drugs.
- D. **Combination Drug Therapy for Hypercholesterolemia**
 1. Bile acid sequestrants may be combined with nicotinic acid or statins to reduce LDL cholesterol by 40-50%.
 2. Bile acid sequestrants can bind to statins, and these drugs should be taken 2-3 hours after taking cholestyramine or colestipol.

V. Hypertriglyceridemia

- A. Elevated serum triglycerides are not an independent risk factor for CHD. Those with triglyceride levels in excess of 1,000 mg/dL are at increased risk for acute pancreatitis.
- B. For severe hypertriglyceridemia, >1000 mg/dL, gemfibrozil is the drug of first choice.

References: See page 148.

Type I Diabetes Mellitus

I. Pathophysiology of Type I (Insulin Dependent) Diabetes

- A. The peak incidence of type I diabetes occurs at age 15. Most patients have developed hyperglycemia by age 30, but a few patients may present at an older age.
- B. Chronic hyperglycemia is associated with the chronic microvascular complications, including retinopathy, nephropathy, and neuropathy.

II. Diagnosis

- A. Insulin-dependent (type I) diabetes mellitus typically presents with severe dehydration, diminished mental status, coma (ketoacidosis), elevated blood glucose, elevated blood acetone, and low blood pH.
- B. Polyuria, polydipsia, polyphagia, weight loss, frequent bacterial or fungal mucocutaneous infections, or blurred vision may occur.
- C. **Physical Findings.** Dehydration (orthostatic hypotension), coexisting infection, and acetone odor on breath.
- D. **Diagnostic Tests**
 1. Generally the diagnosis of type I diabetes may be confirmed immediately by fingerstick blood glucose and urine dipstick ketone testing.
 2. Blood glucose is usually greater than 250 mg/dL. Oral glucose tolerance testing is not necessary.

3. Glycohemoglobin may be elevated, but the short duration of hyperglycemia in many type I diabetics prior to diagnosis, precludes this test from being helpful.

III. Differential Diagnosis

- A. The only two common causes of chronic hyperglycemia are type I and type II diabetes mellitus. They are distinguished by the presence of ketosis in type I diabetes.
- B. Age of onset is a less reliable indicator, because a subset of type II diabetics present as teenagers, and type I diabetes may present at any age.

IV. Treatment Strategy

- A. All type I diabetics should immediately be started on insulin injections when the diagnosis is made.
- B. At the initial diagnosis, the goals of therapy can be defined more loosely.
- C. **Diet**
 1. 60% of calories should be carbohydrate, 20% protein, and no more than 20% as fat. Cholesterol intake should be less than 300 mg/day.
 2. High-fiber foods and artificial sweeteners should be encouraged.
 3. Diet should be consistent from day to day, and meals should not be skipped.

V. Intensive Insulin Therapy

- A. The Diabetes Control and Complications Trial Study demonstrated that improved glycemic control is important for preventing diabetic complications (retinopathy, nephropathy, neuropathy).
- B. Intensive insulin therapy aimed at tight glucose control is recommended, except in patients with recurrent severe hypoglycemia or hypoglycemic unawareness, or patients with far advanced complications (renal failure), or patients with coronary artery disease or cerebral vascular disease, or children younger than age 13.
- C. The general goal of insulin therapy is to control the blood glucose at a level as close to normal as is possible.
- D. Severe acute hypoglycemia can result in seizures, coma, irreversible brain damage, myocardial infarction, and death.

VI. Monitoring

Target Blood Glucose Levels for Patients with IDDM

	Before Meals mg/dL	After Meals	Glycosylated Hemoglobin
Intensive therapy	70-120	<180	7%
Usual therapy	160-200	<200	8-9%
Elderly	<160	<200	9-10%

A. Home Blood Glucose Monitoring

1. Initially, diabetics should check their blood sugar levels prior to each meal, at bedtime, and at least once a week at 3 AM to detect asymptomatic hypoglycemia. Patients should also periodically monitor their blood sugar 1-2 hours after eating to make certain that the preprandial dose of regular insulin was appropriate for that meal.
2. Stable patients may be monitored by one test per day performed at rotating times.

B. Glycosylated Hemoglobin

1. The percentage of hemoglobin A1 molecules which are glycosylated is dependent on mean blood glucose level and is a marker of the mean blood glucose concentration during the previous 60-120 days.

2. The Hb A1c level should be tested in stable patients every 3 to 4 months.

VII. Insulin Regimens

- A. An insulin regimen must provide (1) basal insulin to suppress background glucose production by the liver, and (2) bolus insulin (given before meals) to limit postprandial glucose elevation.
- B. Doses of human regular insulin are either added to or deleted from the basic insulin regimen to bring the next blood glucose value into target range.

Pharmacokinetics of Commonly Used Human Insulins

Insulin type	Onset (hr)	Peak (hr)	Duration (hr)	Maximum duration (hr)
Regular	1/2-1	2-3	3-6	4-6
NPH	2-4	4-10	10-16	14-18

- C. **Estimation of Total Daily Insulin Dose.** Prior to designing an insulin regimen, the estimated total daily insulin dose should be calculated.

Total Daily Dose of Insulin = Weight in kg (0.5 - 0.7 U/kg)

- D. **Regular Human Insulin** is injected 15-30 minutes before meals. Blood testing 1 hour postprandially and just before the next meal helps determine the appropriate dose. Regular insulin has an onset within 1 hour and a duration of 3-6 hours.
- E. **NPH Insulin.** Intermediate-acting insulins are used to provide basal insulin. The effect of intermediate insulins can best be monitored by determining pre-dinner and fasting blood glucose levels. Onset of action occurs at 2 hours and peak occurs at 4 to 10 hours; duration of action is 14-18 hours.
- F. **Insulin Lispro (Humalog)** is a formulation of human insulin with a more rapid onset and a shorter duration than regular insulin. Insulin lispro should be used within 15 minutes of meals.
- G. **Premixed Insulin Preparations.** The 70/30 preparation is 70% NPH and 30% regular insulin, and the 50/50 preparation is 50% NPH and 50% regular insulin. Premixed preparations can be helpful in treating children and older individuals who have difficulty mixing insulin.
- H. Subcutaneous insulin remains standard therapy. Other methods for insulin delivery include pen injectors, jet injectors, and continuous subcutaneous infusion pumps.

I. NPH/Regular Insulin Regimens

1. **Twice Daily Therapy** consists of NPH and regular insulin twice a day; it is the most frequently used regimen. Its main advantage is simplicity. Its disadvantage is that nighttime hypoglycemia is common. Two-thirds of the daily insulin dose is given before the breakfast, and one-third is administered before dinner. 2/3 of total insulin requirement is given as NPH and 1/3 as regular.
2. **Thrice Daily Therapy** moves NPH insulin to bedtime to avoid nighttime hypoglycemia and to control the fasting blood glucose level better.

Most Common NPH/Regular Insulin Regimens

	Morning	Evening	Bedtime
Twice Daily Regimen	NPH/regular	NPH/regular	
Thrice Daily Regimen	NPH/regular	Regular	NPH

J. Control of High Fasting Glucose Levels

- Causes of a high fasting blood glucose level in a patient on a twice daily regimen include the following:
 - Insufficient basal insulin overnight.
 - Excessive basal insulin, resulting in hypoglycemia at 2 AM, and leading to a rebound increase of fasting glucose (Somogyi effect).
 - The "dawn phenomenon" (increased early morning glucose secondary to morning cortisol secretion).
- In patients with high fasting blood glucose, before a change is made in the insulin schedule, blood glucose at 2 to 3 AM are determined. If the glucose level is low at this time, the amount of evening NPH insulin should be decreased or the injection moved to bedtime. If the glucose value is elevated, the amount of evening NPH insulin should be increased. Doses should be adjusted 1 or 2 units at a time.

VIII. Supplementation of Insulin Dosage

- Once the basic insulin regimen has been established, insulin supplements can be used with the goal of bringing the next scheduled glucose determination into target range.
- If supplements are consistently needed at a particular time of day the basic insulin dose is increased.

Insulin Sliding Scale for Supplementation

Post-Prandial Blood glucose level	Preprandial Action Needed
<70	Reduce regular insulin by 1-2 units
71-120	Take prescribed amount of insulin
121-150	Increase regular insulin by 1 unit
151-200	Increase regular insulin by 2 units
201-250	Increase regular insulin by 3 units
>250	Increase regular insulin by 4 units

- If the planned meal is larger than usual, increase preprandial regular insulin by 1 to 2 units. If the planned meal is smaller than usual, decrease preprandial regular insulin by 1 to 2 units.

IX. Chronic Complications of Diabetes

- Retinopathy.** Ophthalmologic evaluation should be performed annually in patients who have had diabetes for 5 years or more, and in patients older than 30. Unexplained changes in vision or funduscopy should be referred to an ophthalmologist.

B. Nephropathy

1. 10-20% of patients with type I diabetes develop end-stage renal failure and require dialysis. The complete syndrome includes proteinuria, hypertension, edema, and renal insufficiency.
2. At the microalbuminuria stage, the renal disease can probably be reversed.
3. **Microalbuminuria Screening**
 - a. Urine albumin/creatinine ratio should be checked annually.
 - b. If albumin is high--exceeding 30 mg/g on at least two occasions--the adequacy of blood sugar and hemoglobin A1c levels should be reevaluated.
 - c. If glycemic control is the best that can be achieved, an ACE-inhibitor should be initiated, even if the patient's blood pressure is normal. Any ACE-inhibitor can be used.

C. Peripheral Neuropathy

1. Neuropathies have an insidious onset and generally progress from the most distal to the more proximal areas of the body.
2. Persistent painful neuropathies may be treated with amitriptyline (Elavil) 25-75 mg po hs and nonsteroidal anti-inflammatory drugs.
3. Pentoxifylline (Trental), 400 mg four times a day, and capsaicin (Zostrix) applied topically prn may provide some relief.
4. Any evidence of tissue breakdown or infection of the feet should be treated aggressively and requires early podiatric consultation.

D. Autonomic Neuropathy

1. Signs of cardiovascular autonomic neuropathy include resting tachycardias, exercise intolerance, painless myocardial infarction, and orthostatic hypotension.
2. Signs of GI autonomic neuropathy include upper GI discomfort (reflux), autonomic gastropathy with delayed gastric emptying, diabetic diarrhea, severe constipation, and fecal incontinence. GI autonomic neuropathy can be assessed by radionucleotide gastric emptying studies.

X. Cardiac Risk Factors

- A. Hyperlipidemia should be screened for and more aggressively. Screening includes HDL, LDL cholesterol, and triglycerides. Levels should be checked after good diabetic control has been obtained because hyperglycemia can raise LDL cholesterol.
- B. Exercise stress test screening is indicated for asymptomatic patients with diabetes for more than 10 years or if other risk factors for coronary disease are present.

References: See page 148.

Type II Diabetes Mellitus

Type II diabetes mellitus is characterized by hyperglycemia and a marked predilection for long-term microvascular, macrovascular and neurologic complications. 90% of diabetics have Type II disease, which is characterized by older age of onset.

I. Pathophysiology

- A. In type II diabetes, impaired insulin secretion and peripheral insulin resistance cause hyperglycemia.
- B. Most patients are over age 50, overweight, and have a strong family history of diabetes.
- C. The Diabetes Control and Complications Trial (DCCT) showed that tight glycemic control reduces the risk of onset and progression of retinopathy and nephropathy by 50-75% in patients with type I diabetes. Complications of type II diabetes also respond to tight control. Tight control requires that patients be highly motivated; however, most diabetic patients do not fit this

description.

II. Diagnosis of Type II Diabetes

- A. A complete lack of symptoms is a very common presentation of type II diabetes. Patients have been hyperglycemic several years prior to diagnosis, and diabetes is often first detected by a screening urinalysis, obtained for other reasons.
- B. Patients rarely exhibit the classic clinical picture of polydipsia, polyuria, weight loss, and blurred vision. Patients may have fatigue and a vague sense of "not feeling well." Female patients may present with vulvovaginitis or fungal infections of the intertriginous areas.
- C. A glycosylated hemoglobin more than 2 standard deviations above normal will establish the diagnosis of diabetes.
- D. Two fasting serum glucose values in excess of 140 mg/dL, or a random serum glucose value in excess of 200 mg/dL will also establish the diagnosis.
- E. Type I diabetes is distinguished from type II by the young age of onset and by the production of ketones in type I diabetes.

III. Initial Evaluation of Type II Diabetics

- A. A history and physical examination should be completed with emphasis on the eye (visual acuity, cataracts, macular edema, retinopathy), the feet (neuropathy and vasculopathy), and blood pressure.

B. Initial Laboratory Evaluation of Patients with Diabetes

Fasting plasma glucose

Glycosylated hemoglobin

Fasting lipid profile (checked after glucose has been controlled)

Electrolytes, BUN, creatinine, liver function tests

Urinalysis (glucose, ketones, protein, sediment)

Microalbuminuria (spot urine albumin/creatinine ratio).

ECG

Goals in Diabetes Mellitus

	Before Meals mg/dL	After Meals	Glycosylated Hemo- globin
Most Patients	70-140	<180	8-9%
Elderly	<160	<200	9-10%

IV. Dietary Management of Type II Diabetes

A. Dietary Therapy of Diabetes Mellitus

1. Calculate Ideal Body Weight

Build	Women	Men
Medium	Allow 100 lbs for 5 feet of height. Add 5 lbs per additional inch	Allow 106 lbs for 5 feet of height. Add 6 lbs per additional inch
Small	Subtract 10%	Subtract 10%
Large	Add 10%	Add 10%

2. **Estimate Basal Caloric Requirement (BCR)** = 10 (IBW) + Activity calories

a. **Activity Calories:** Sedentary, add 10% of BCR; Moderate, add 20% of BCR; Strenuous, add 40-100% of BCR

b. **Weight Loss:** Subtract 500 kcals/day to achieve 1 lb/week

78 Type II Diabetes Mellitus

weight loss

3. American Diabetes Association Diet

- a. Carbohydrates = 55-60% total calories
- b. Protein = 25-30% total calories
- c. Fat = <30% total calories
- d. Saturated fat = <10% total calories

B. Weight Reduction will ameliorate insulin resistance and may prevent the need for hypoglycemic drugs.

V. Hypoglycemic Drug Treatment of Type II Diabetes

A. Sulfonylureas are used in monotherapy and in combination with metformin or insulin. They lower blood glucose levels by stimulation of beta cells and by lowering peripheral and hepatic insulin resistance.

1. The principal side effect is hypoglycemia, usually caused by increased exercise or delayed meals. Episodes are easily treated with food.
2. Sulfonylureas are available in generic form, except Glynase PresTab, Glucotrol XL, and Amaryl.
3. **Contraindications to Oral Hypoglycemic Therapy.** 1) type I diabetes, 2) pregnancy and lactation, 3) severe concurrent diseases, such as sepsis or trauma, where insulin is required.
4. **Glipizide (Glucotrol).** Initial dose 5 mg qd. Increase slowly over weeks to 20 mg bid, according to blood glucose response. **Glucotrol XL** may be taken as a single daily dose of 5 or 10 mg (max 20 mg/day); contraindicated in renal insufficiency.
5. **Glyburide (DiaBeta, Glynase PresTab, Micronase).** Initial dosage 2.5 mg qd. Increase slowly over weeks up to 10 mg bid, according to glucose response. Contraindicated in renal insufficiency.
6. **Glimepiride (Amaryl)** 1-4 mg PO qd, max 8 mg/day [1, 2, 4 mg]; it offers no advantages compared to other sulfonylureas.

B. Biguanides--Metformin (Glucophage)

1. Metformin lowers blood glucose levels by decreasing peripheral and hepatic insulin resistance.
2. Major advantages are the absence of hypoglycemia and a favorable effect on weight loss.
3. **Contraindications to Metformin Therapy**
 - a. Renal dysfunction (creatinine 1.4 mg/dL)
 - b. Liver dysfunction
 - c. History of alcohol abuse or binge drinking
 - d. Acute or chronic metabolic acidosis
 - e. Conditions predisposing to renal insufficiency and/or hypoxia:
 - (1) Cardiovascular collapse
 - (2) Acute myocardial infarction or acute congestive heart failure
 - (3) Severe infection
 - (4) Use of iodinated contrast media
 - (5) Major surgery
4. Starting dosage is 850 mg with the evening meal or 500 mg bid with meals; the dose is titrated up to a maximum of 850 mg tid with meals.
5. Metformin can be used as monotherapy for type II diabetes and as combination therapy with a sulfonylurea or a alpha-glucosidase inhibitor. Combination therapy is especially successful in obese, insulin-resistant patients. If it is administered with a sulfonylurea, the sulfonylurea should be administered at half the maximum (or previous) daily dose, taken in the morning.
6. **Side Effects**
 - a. Major side effects are diarrhea, nausea, vomiting, and a metallic taste. These side effects usually disappear with time.
 - b. Lactic acidosis is rare and has an incidence of 0.03 cases per 1,000 patient years.

C. Alpha-glucosidase Inhibitors--Acarbose (Precose)

1. Acarbose delays the breakdown and absorption of carbohydrate in the

gut, resulting in decreased glucose levels.

2. Although it may be used alone, acarbose is most effective when used in combination with a sulfonylurea, where it may be expected to decrease glycosylated hemoglobin by 0.75-1.0 %. Acarbose may be used with metformin.
3. It does not cause lactic acidosis or hypoglycemia.
4. **Dosage.** 25-100 mg tid with the first bite of the meal [25, 50, 100 mg].
5. **Side effects** include dose-related diarrhea in 40% and a mild transaminase elevation.

VI. Treatment Regimens for Type II Diabetes

A. Monotherapy

1. **A sulfonylurea** is initial monotherapy for most patients. They can be given once a day initially. Maximum effectiveness is reached when given twice a day.
2. **Metformin** monotherapy may be of greater advantage in morbidly obese, insulin-resistant patients. It may be less effective in thin patients, who may be more insulin-deficient.
3. **Acarbose** can be used as monotherapy in any patient with mild type II diabetes. It is safe and is of value as a first-line drug in elderly patients, those with a mild elevation of Hb A1c, or those in whom metformin and sulfonylureas are contraindicated. It decreases Hb A1c to a lesser degree than sulfonylureas and metformin. Patients who fail to respond to acarbose monotherapy should be switched to a sulfonylurea or metformin.
4. Patients who do not respond to sulfonylurea or metformin monotherapy should be changed to combination therapy.

B. Combination Therapy

1. Combination therapy may be accomplished with a sulfonylurea and metformin, or with acarbose and either a sulfonylurea or metformin.
2. For severe hyperglycemia and an Hb A1c value over 10%, combination therapy with insulin and either a sulfonylurea or metformin or acarbose is optimal.

C. Insulin Therapy

1. Insulin therapy almost inevitably results in weight gain (average of 10-15 pounds) which may exacerbate hypertension and hyperlipidemia. High-dose insulin has been shown to be atherogenic in animal models. Increasing insulin dosages above 1 unit/kg/day is unlikely to provide additional improvement in hyperglycemia, though it will contribute to further weight gain and dyslipidemia.
2. **Insulin plus Oral Hypoglycemic Agent (OHA) Therapy**
 - a. **OHA/NPH Insulin Regimen:** Most effective in diabetics who weigh <150% of ideal body. A half-maximal dose of oral hypoglycemic agent is given before breakfast and 10-20 units NPH insulin are given at bedtime.
 - b. **OHA/NPH Insulin/Regular Insulin Regimen:** More effective for obese patients who consume large evening meals. A half-maximal dose of oral hypoglycemic is given in the morning and 10-20 units of premixed (70% NPH/30% regular) insulin is given before supper.
3. **Insulin Monotherapy**
 - a. **Single daily injections** of intermediate-acting (NPH) insulin may be appropriate for newly-diagnosed patients who are not yet absolutely insulin deficient, older patients with renal insufficiency who require only small doses of insulin, and patients with poor vision or poor motivation who cannot administer multiple daily injections. If a morning dose of 0.5-1 unit/kg is insufficient to prevent significant nocturnal hyperglycemia, an evening dose should be added.
 - b. **Twice-daily Insulin** is the most commonly used regimen. It is initiated by calculating the total daily insulin requirement (0.5-1 unit/kg/d) and giving 2/3 of the total dose in the morning and 1/3 in the evening; 2/3

of each dose is NPH and 1/3 is regular insulin.

4. Management of Insulin Resistance

- a. Troglitazone (Rezulin) is indicated in patients with type II diabetes who are not adequately controlled on insulin (Hb A1c >8.5%). It increases insulin uptake by skeletal muscles and decreases hepatic gluconeogenesis; must be used concurrently with insulin. Initial dose 200 mg PO qd x 2-4 weeks, then 400 mg PO qd; max 600 mg qd [200, 400 mg tabs]; elevations of LDL and HDL may occur, and hemoglobin may decrease by 3-4%.

VII. Therapeutic Monitoring

- A. Most stable type II diabetics treated with oral hypoglycemic agents may be adequately monitored with quarterly glycohemoglobin (Hb A1c) testing and office glucose checks.
- B. Insulin-treated type II diabetics should perform daily home blood glucose testing. Stable patients may be monitored by one test per day performed at rotating times.

VIII. Complications of Type II Diabetes

- A. **Heart Disease, Stroke, and Peripheral Vascular Disease** occur earlier and with greater frequency in diabetics. Angina is less likely to be symptomatic because of autonomic nervous system insufficiency.

1. Treadmill stress tests are obtained for patients with risk factors for coronary artery disease.
2. Hyperlipidemia should be treated more aggressively. Niacin raises blood glucose and is contraindicated in diabetes.
3. Aspirin therapy reduces stroke and cardiac risk.

B. Hypertension

1. Hypertension should be treated more aggressively in diabetics. The angiotensin-converting enzyme inhibitors are the agents of first choice because they do not adversely affect glycemic or lipid profiles, and they have a protective effect on diabetic nephropathy.
2. Alpha blockers (terazosin, doxazosin) are second line agents because they do not adversely affect glucose or lipids.
3. Thiazide diuretics should be avoided because they can raise glucose levels and adversely affect lipids.
4. Beta blockers should be avoided because they adversely affect glucose control and lipids and may mask the symptoms of hypoglycemia.

C. Retinopathy

1. 50% of diabetics have some degree of retinopathy after 10 years. 80% of all diabetics will have retinopathy 15 years after diagnosis.
2. A dilated pupillary exam by an ophthalmologist should be done at baseline evaluation and yearly after 5 years of diabetes. Any rapid deterioration of visual acuity should be referred for ophthalmologic evaluation.
3. Proliferative retinopathy and hemorrhages lead to a loss of vision and dictate urgent ophthalmologic consultation.

D. Nephropathy

1. In patients older than 40, the incidence of diabetic renal disease is 5-10%.
2. Significant renal disease is heralded by the onset of microalbuminuria, which in turn leads to proteinuria and eventually to an elevated creatinine.
3. At the level of microalbuminuria, nephropathy can be reversed through careful diabetic control, aggressive treatment of hypertension, and avoidance of nephrotoxic drugs, including NSAIDs.

4. Microalbuminuria Screening

- a. Urine albumin/creatinine ratio should be checked annually.
- b. If albumin is high--exceeding 30 mg/g on at least two occasions--the adequacy of blood sugar and Hb A1c levels should be reevaluated.
- c. If glycemic control is the best that can be achieved, an ACE-inhibitor should be initiated, even if the patient's blood pressure is normal. Any ACE-inhibitor can be used.

- E. Neuropathy.** Foot problems are common in diabetics. They should regularly inspect their feet, and a foot examination should be a part of every clinic visit, including an assessment for neuropathy, vasculopathy, ulcers, or infection. A microfilament sensory test detects early neuropathy.

References: See page 148.

Low Back Pain and Osteoarthritis

I. Initial Classification of Acute Low Back Symptoms

- A. Sciatica.** Back-related, lower limb symptoms suggest lumbosacral nerve root compromise.
- B. Nonspecific Back Symptoms** occur primarily in the back and suggest neither nerve root compromise nor a serious underlying condition.
- C. Potentially Serious Spinal Conditions.** Tumor, infection, spinal fracture, or a major neurologic compromise, such as cauda equina syndrome.
- D.** In the absence of signs of dangerous conditions, special studies are not required since 90% of patients will recover spontaneously within 4 weeks.
- E. Nonmechanical Causes of Low Back Pain**
 - 1. Rheumatologic Disease.** Polymyalgia rheumatica, fibrositis, ankylosing spondylitis, Reiter's syndrome, psoriatic arthritis, enteropathic arthritis.
 - 2. Infection.** Vertebral osteomyelitis, diskitis, epidural abscess
 - 3. Tumor.** Osteoma, multiple myeloma, skeletal metastases.
 - 4. Endocrinologic and Metabolic Disorders.** Osteoporosis with fracture, osteomalacia.
 - 5. Referred Pain.** Abdominal aortic aneurysm, kidney stone, pyelonephritis.

Markers for Potentially Serious Conditions

Fracture	Tumor or Infection	Cauda Equina Syndrome
Major trauma, such as a vehicle accident or a fall from height. New onset or worsening of back pain after minor trauma or strenuous lifting in an older or osteoporotic patient.	Age >50 or <20. History of cancer, fever, chills, weight loss. Pain worsens at rest or when supine; severe nighttime pain. Risk Factors for Spinal Infection: Recent bacterial infection, UTI, IV drug abuse, diabetes, immunosuppression.	Saddle anesthesia. Bladder dysfunction (urinary retention, frequency, overflow incontinence). Severe or progressive neurologic deficit in the lower extremity. Laxity of the anal sphincter. Perianal/perineal sensory loss. Major motor weakness.

II. Clinical Evaluation of Low Back Pain

- A.** Assess present symptoms, limitations, duration of symptoms, and history of previous episodes of pain or injury. Symptoms may include constant or intermittent pain, numbness, weakness, and stiffness located primarily in the back, leg, or both.
- B.** Ascertain results of any previous testing or treatment.
- C.** Sudden onset of pain is most likely to arise from a disk, while pain with a slow onset or with frequent, milder recurrences, is more likely to be ligamentous in origin.
- D.** Certain body positions or movements may exacerbate or relieve pain. Determine the time of day when pain appears. Herniated disk pain causes great difficulty sitting or bending, while pain of ligamentous origin causes inability to remain in any position for a long time without moving to relieve the pain.
- E.** Obtain an occupational and recreational history; assess degree of disability

82 Low Back Pain and Osteoarthritis

and modifications of activity. Determine how much weight the patient can lift.

- F. Spinal stenosis is associated with vague bilateral leg pain that occurs with walking or standing.

III. Physical Examination

- A. Severe guarding of lumbar motion in all planes may indicate spinal infection, tumor, or fracture.
- B. Vertebral point tenderness to palpation may suggest fracture or infection.
- C. Range of motion of the back (disk problems tend to limit range of motion asymmetrically) is assessed. Ask patient to bend forward, backward, and from side to side, noting pain.
- D. Palpate the back to identify tender areas or trigger point areas over the interspinous, posterior sacroiliac, and iliolumbar ligaments. Disk problems often cause very little tenderness, while chronic ligament strains cause specific tender points.

E. Neurologic Screening

1. Testing for Muscle Strength

- a. Ask patient to toe walk (calf muscles, S1 nerve root), heel walk (ankle and toe dorsiflexor muscles, L5 and some L4 nerve roots), squat and rise (quadriceps, L4 nerve root).
- b. Test the dorsiflexor muscles of the ankle or great toe (L5 or some L4 nerve root), hamstrings and ankle evertors (L5-S1), and toe flexors (S1).

- 2. **Circumferential Measurements.** Muscle atrophy can be detected by measurements of calf and thigh circumference. Differences of more than 2 cm are abnormal.

- 3. **Reflexes.** Ankle jerk reflex tests the S1 nerve root; knee jerk reflex tests the L4 nerve root.

- 4. **Sensory Examination.** Light touch is tested in the medial (L4), dorsal (L5), and lateral (S1) aspects of the foot.

F. Testing for Sciatic Tension

- 1. Straight leg raising (SLR) test can detect tension on the L5 and/or S1 nerve root related to disc herniation.
- 2. Sitting knee extension tests sciatic tension in the same way as SLR. Patients with significant nerve root irritation will have pain or will lean backward.
- G. Anal sphincter tone and sphincter reflex (scratching perianal area and watching for constriction) should be tested. Intact perianal innervation indicates intact bladder innervation. Failure to detect impairment of bladder innervation may result in permanent bladder hypotonicity.

IV. Initial Treatment of Low Back Pain

A. Nonsteroidal Anti-inflammatory Drug Therapy

- 1. When short-term analgesia is the primary goal, the key consideration is rapid onset. Athletic injuries and soft-tissue trauma are common conditions which require a rapid-onset NSAID.
- 2. In patients with chronic mild to moderate pain, intermediate- and long-acting NSAIDs may improve compliance because of once- or twice-daily dosing. They are not recommended in the elderly or those with compromised renal or hepatic function because of a greater risk of toxic accumulation. Long-acting NSAIDs are not useful for more severe pain.
- 3. The newer NSAID drugs nabumetone and etodolac have not been reported to produce as many GI adverse effects. NSAIDs should be taken with food to reduce GI upset.
- 4. A loading dose of twice the standard dose will result in a more rapid onset of action.
- 5. NSAIDs should be prescribed with caution in patients being treated with antihypertensives or anticoagulants.

Dosages for NSAIDs with half-life <4 h

Drug and Maximum Dosage	Dosage
Ibuprofen (Motrin) 3,200 mg/d	400 mg, 600 mg, or 800 mg tid or qid; usually the agent of choice [200, 300, 400, 600, 800 mg]
Ketoprofen (Orudis) 300 mg/d	25-75 mg tid-qid [25, 50, 75, mg]
Tolmetin (Tolectin) 2,000 mg/d	400 mg tid to start; 600-1,800 mg/d in 3-4 divided doses [200, 400, 600 mg]
Ketorolac (Toradol) 40 mg/d	30-60 mg IM/IV, followed by 15-30 mg IM/IV q6h; max 120 mg/day; or 10 mg PO q6h prn [10 mg].

Dosages for NSAIDs with Half-Life >5 h

Half-Life 5-15 h	
Diflunisal (Dolobid) 3,200 mg/d	1000 mg, followed by 500 mg q8-12h [250, 500 mg]
Etodolac (Lodine) 1,200 mg/d	200-400 mg q6-8h [200, 300, 400 mg]
Ketoprofen, extended release (Oruvail) 300 mg/d	200 mg once a day [100, 150, 200 mg]
Naproxen sodium (Anaprox, Aleve) 1,375 mg/d	550 mg, followed by 275 mg bid-tid [275, 550 mg-SR]
Naproxen (Naprosyn) 1,250 mg/d	500 mg, followed by 250-500 q6-8h. [250, 375, 500 mg]; slower onset than naproxen sodium.
Half-Life >15 h	
Nabumetone (Relafen) 2,000 mg/d	Starting dose, 1,000 mg, then 500-750 mg qd-bid. [500, 750 mg].
Piroxicam (Feldene) 20 mg/d	10-20 mg qd [10, 20 mg]

B. Management of NSAID Therapy

1. Patients receiving NSAIDs over a long period of time should be monitored for occult blood loss. A hematocrit is obtained at baseline, and repeated every 6-12 months. A chemistry profile, including electrolytes and urinalysis, are recommended if an NSAID is to be used chronically.
2. Hepatic toxicity from NSAID therapy occurs less frequently than renal toxicity. Liver function tests should be done at 6-12-month intervals.
3. If the desired effect is not achieved after two weeks, consider an increase in dosage. If the therapy is still unsatisfactory, switch to another NSAID with a similar half-life.

4. If full dosages of an NSAID fail to provide adequate relief, consider adding acetaminophen 650-1,000 mg q4h concurrently; the effect of both drugs may be synergistic. Acetaminophen spares the gastric mucosa, but has the potential for hepatic toxicity.
5. An NSAID may be used in conjunction with propoxyphene (Darvon) or another narcotic analgesic, with the NSAID taken regularly and the narcotic agent taken prn.

C. Lessening the Risk of Gastric Ulceration

1. Misoprostol (Cytotec) is the agent of choice to prevent NSAID-induced gastric ulcers in high-risk patients; diarrhea is common. Contraindicated in pregnancy, irritable bowel syndrome. The dosage of misoprostol should usually be adjusted from a test dosage of 100 mcg 2-4 times daily taken with food. Recommended dosage is 100-200 mcg qid.

D. Muscle Relaxants. Muscle relaxants are no more effective than NSAIDs for low back symptoms, drowsiness is common.

1. Cyclobenzaprine (Flexeril) 10 mg PO tid [10 mg].
2. Methocarbamol (Robaxin) 500-750 mg PO bid-tid [500, 750 mg].
3. Carisoprodol (Soma) 350 mg PO tid-qid [350 mg]

E. Antidepressants

1. Patients with chronic pain frequently benefit from amitriptyline (Elavil) 25-75 mg qhs, or another tricyclic, in addition to their pain medication.
2. Imipramine (Tofranil) may also offer pain relief 50-150 mg PO qhs [10, 25, 50 mg], fluoxetine (Prozac) may also be useful; 20 mg PO qAM.

V. Physical Methods

A. Activity Alteration

1. Most patients will not require bed rest. Prolonged bed rest (more than 4 days) has potentially debilitating effects. Two to four days of bed rest are reserved for patients with the most severe limitations.
2. Patients can minimize the stress of lifting by keeping any lifted object close to the body at the level of the navel. Twisting, bending, and reaching while lifting also increase stress on the back. Patients should avoid prolonged sitting. A soft support placed at the small of the back, and armrests to support some body weight, may make sitting more comfortable.
3. After acute inflammation has subsided, extension and flexion exercises should be used to increase strength and flexibility. Aerobic exercise such as walking, swimming, and light jogging may be recommended.

B. Traction applied to the spine is not effective for treating acute low back symptoms. Massage, diathermy, ultrasound, biofeedback, transcutaneous electrical nerve stimulation (TENS), low back corsets and back belts have no proven efficacy.

C. Needle acupuncture and injection of steroids or lidocaine into the epidural space have no proven benefit.

D. Soft shoe insoles are an option for patients who must stand for prolonged periods.

VI. Special Diagnostic Studies

A. Routine testing and imaging studies are not necessary during the first month of back symptoms except when there is a suspicion of a dangerous condition. If a patient's limitations, due to low back symptoms, do not improve in 4 weeks, reassessment and further diagnostic studies may be indicated.

B. Laboratory Tests. Erythrocyte sedimentation rate, complete blood count, and urinalysis (UA) can be useful to screen for suspected infection, tumor, or rheumatologic conditions.

C. Imaging: MRI or CT-scan should be considered if there are nerve findings on physical examination or when surgery is being considered.

D. Lumbosacral radiographs are usually not helpful.

E. Bone Scanning is rarely useful, but can detect suspected spinal tumors, infection, or occult fractures.

F. Electromyography (EMG) may be useful to identify focal neurologic dysfunction in patients with leg symptoms.

G. Sensory Evoked Potentials (SEPs) may be indicated if spinal stenosis or spinal cord myelopathy is suspected.

VII. Surgical Considerations

A. Criteria for Nerve Root Decompression

1. Sciatica is both severe and disabling.
2. Symptoms of sciatica persist without improvement for longer than 4 weeks or with extreme progression.
3. There is strong evidence of dysfunction of a specific nerve root with intervertebral disc herniation confirmed by an imaging study.

B. Surgery is an elective procedure unless progressive motor deficits, cauda equina syndrome or other emergency is present.

C. Urgent orthopedic referral is recommended for severe, unremitting leg pain is unresponsive or if significant acute neurologic deficits are present, especially in the distribution of S1 and S2 (because of the risk of bladder hypotonicity).

References: See page 148.

Dermatologic Disorders

Acne Vulgaris

I. Clinical Manifestations

- A. Acne comedones are usually found on the forehead and upper cheeks of adolescents. Comedones may progress to inflammatory lesions on the lower cheeks, chin, chest, upper back, and shoulders.
- B. In females, the possibility of androgenic disorders such as polycystic ovarian disease and Cushing's syndrome should be considered; the patient should be asked about menstrual irregularities and should be examined for hirsutism.

II. Non-Pharmacologic Therapy for Acne

- A. **Diet.** Patients should be advised to eat a well-balanced diet and to avoid foods which consistently result in acne flare-ups.
- B. **Cleanliness**
 1. Development of acne is not related to dirt. Excessive scrubbing, especially with abrasive cleaners and sponges, may worsen the condition.
 2. Patients who have oily skin should wash their faces using mild, unscented, antibacterial soap (Dial, Lever-2000) and water.
- C. **Environment.** Very humid environments, heavy sweating, or exposure to pollution may aggravate acne.
- D. **Mechanical Trauma.** Pressure, rubbing, and humidity from occlusive clothing can aggravate acne. Repeated picking of lesions can cause increased inflammation, scarring, and pigmentary changes.
- E. **Cosmetics.** Heavy oils, greases or dyes in cosmetic creams and hair sprays can exacerbate acne. Water-based products should be used.
- F. **Medications that Worsen Acne.** Corticosteroids, androgens, phenytoin, lithium, isoniazid, and cyclosporine. Oral contraceptives with androgenic progestones may promote acne.

III. Pharmacologic Therapy

A. Treatment of Comedonal Acne

1. Mild noninflammatory acne can be treated with topical antibacterial agents such as benzoyl peroxide or comedolytic agents such as tretinoin (Retin-A). The combination of benzoyl peroxide in the morning and tretinoin at night is effective.
2. Creams and lotions usually are less drying than gels and liquids.
3. **Benzoyl Peroxide**
 - a. Potent antibacterial, mild comedolytic and exfoliant properties.
 - b. Benzoyl peroxide is first-line therapy for mild acne, and may be used with other agents. Available over-the-counter as 2.5%, 5%, and 10% gels, creams, lotions or soaps. The liquids and creams (Benoxyl, Oxy-10) are less irritating and are useful for dry skin. The gel (Benzagel, Persa-Gel, Desquam-X) is more irritating but more effective for oily skin. Mild redness and scaling occurs during the first week.
 - c. The 5% strength is less irritating than the 10% strength and equally effective. Apply qAM-bid after washing [2.5, 5-10% gel, 5-10% cream or lotion].
4. **Tretinoin (Retin A)** is the most effective topical comedolytic agent.
 - a. Retin-A cream (0.025, 0.05, 0.1%) [20, 45 g]; Retin-A gel (0.01, 0.025%) [15, 45 g]; or Retin-A liquid (0.05%) [28 mL].
 - b. Start with 0.025% cream or gel. If no response occurs after a few weeks, a higher-concentration is used. The cream is best for dry skin;

the gel is best for oily skin.

- c. It should be applied once a day at bedtime, 30 minutes after washing (to dry skin).
- d. Mild redness and peeling occurs. Improvement may take 6-12 weeks; avoid excessive sun exposure, and use sunscreen.

5. Azelaic Acid Cream (Azelex)

- a. Azelaic acid cream is indicated for the treatment of mild-to-moderate inflammatory acne in patients who cannot tolerate topical tretinoin (Retin A).
- b. It exerts an anti-acne effect by bacteriostatic activity. Azelaic acid is as effective as tretinoin cream but with less drying side effects. Precaution against sun exposure is not required with azelaic acid, as it is with tretinoin.
- c. Azelaic acid is generally well tolerated. Itching or burning of the skin may occur in 1-5%. Hypopigmentation has been reported.
- d. Azelaic acid cream 20% is applied bid [30 gm] (as opposed to qd for tretinoin). Azelaic acid is twice as expensive as tretinoin.

B. Treatment of Papular Acne

1. Topical antibiotics are useful alone or in combination with benzoyl peroxide, tretinoin, or systemic antibiotics.
2. **Topical Antibiotics**
 - a. **Clindamycin.** Available in 1% solution, lotion or gel (Cleocin-T); apply to affected areas bid after cleansing.
 - b. **Erythromycin.** 2% solution (EryDerm, A/T/S), gel (Erygel, Emgel), or pledgets (Erycette, T-stat); apply to affected areas bid; also available in a 3% gel combined with 5% benzoyl peroxide (Benzamycin) which is the most effective topical antibiotic.

C. Treatment of Pustular Acne

1. Moderate or severe inflammatory acne requires oral antibiotics in addition to topical therapy. Side effects of oral antibiotics include gastrointestinal distress and vaginal candidiasis. Oral antibiotics are continued for 3 months to 2 years or longer. The dosage must be tapered when they are discontinued.
2. **Tetracycline**
 - a. Effective and low cost; first-choice oral antibiotic. Starting dosage is 250 mg qid or 500 mg bid, 1 hour before or 2 hours after meals; after 1-2 months reduce to 250 mg PO qd.
 - b. Antacids or dairy products can interfere with absorption; can cause dental discoloration; contraindicated in pregnancy or in children <12 years; photosensitizing.
3. **Minocycline (Minocin).** Highly effective because of its lipid solubility and ability to penetrate the sebaceous follicle; good absorption with food; high cost. The usual starting dose is 50 mg bid or 100 mg qd [50,100 mg].
4. **Doxycycline.** Less expensive than minocycline and is very effective. 100 mg once daily; photosensitivity, gastrointestinal distress may occur.
5. **Erythromycin.** Starting dosage is 250 mg qid or 500 mg bid. Propionibacterium acnes bacteria are more resistant to erythromycin than tetracycline; gastrointestinal side effects.

D. Treatment of Nodulocystic Acne

1. Isotretinoin (Accutane)

- a. Vitamin A derivative; decreases sebum production and reverses abnormal epithelial desquamation.
- b. **Initial Dose.** 0.5-1.0 mg/kg, or 40-80 mg/day [10,20,40 mg]. The usual duration of therapy is 4-5 months, and the response rate is 90%. Transient exacerbation of acne may occur during the initial month; only one course is usually needed.
- c. **Side Effects.** Cheilitis, dry skin, pruritus, epistaxis, photosensitivity, decreased night vision, hypertriglyceridemia, abnormal liver function tests, electrolyte imbalance, elevated platelet count. Side effects are

usually reversible once therapy is discontinued.

d. Teratogenic: Pregnancy is contraindicated for 1 year. Exclude pregnancy with a monthly serum test; contraception must be used.

2. Systemic Hormones: For female patients, low dose oral contraceptives can suppress ovarian androgen production. Demulen is commonly used.

References: See page 148.

Dermatitis and Verruca Vulgaris

I. Classification of Dermatitis (Eczema)

A. Contact dermatitis is a nonallergic reaction caused by irritating substances.

1. Any substance can act as an irritant, provided the concentration and duration of contact with the skin are sufficient.
2. Irritants include water, soaps and detergents, aluminum salts in deodorants, urine, feces, acids, and alkalis.

B. Delayed Type Hypersensitivity Reactions are immunologic reactions to contact allergens of the delayed hypersensitivity type, occurring in sensitized individuals.

1. Acutely, irritants produce erythema, microvesicles, and oozing, which may be indistinguishable from allergic contact dermatitis. If the agent is strong enough, blisters, erosions, and ulcerations can occur.
2. The interval between introduction of the antigen and development of clinical symptoms varies from 3-12 days on the 1st exposure in a susceptible patient.
3. An already sensitized individual will react to the substance within 12-48 hours.

4. Common Topical Sensitizers

- a. Toxicodendrons (poison ivy, oak, and sumac, ragweed pollen)
- b. Ethylenediamine (a stabilizer in many topical creams)
- c. Nickel (10% of females are allergic to nickel found in jewelry)
- d. Benzocaine

C. Atopic Dermatitis

1. A constitutional and inherited ability to react with pruritus and inflammation of the skin; pathogenesis is unknown.
2. Associated with asthma, hay fever, urticaria, and high levels of IgE.
3. **Clinical Presentation**
 - a. Commonly begins as infantile eczema that presents as dermatitis of the cheeks, face, and upper extremities. This remits or may change to a flexural dermatitis of the antecubital fossae and neck.
 - b. Flexural involvement usually lasts from ages 4-10 years old, but may go on longer.
 - c. Most atopic childhood eczema fades in adult life, but sometimes recurs at times of stress or for unknown reasons. In adults it may appear as recalcitrant hand eczema or as a localized or generalized dermatitis.
4. Atopic skin is particularly susceptible to bacterial and viral infections that may become widespread. These patients may develop widespread herpes infections of the skin, and they should be protected from people with active herpetic lesions.

II. Treatment of Dermatitis/Eczema

- A. Identify and avoid offending agents. Remove the antigen as soon as possible with warm, soapy water.
- B. **Acute Dermatitis that is Wet, Vesicular, or Weeping.** Use wet compresses with either tap water or an antibacterial solution to cleanse the area and soothe itching.
- C. Oral antihistamines such as diphenhydramine or trazodone are useful for

pruritus.

- D. Topical Corticosteroids.** In the intertriginous and facial areas, use only low-potency steroids, such as 1% hydrocortisone cream, as there is risk of causing atrophy in these areas. Stronger steroids should be reserved for other areas of the skin.

E. Low-Potency Topical Corticosteroids

1. Hydrocortisone apply tid-qid [cream 0.5, 1, 2.5%; ointment 0.5, 1, 2.5%; lotion 1, 2, 2.5%].
2. Triamcinolone acetonide (Aristocort, Kenalog) apply to affected area tid-qid [ointment 0.1, 0.5%; cream 0.1, 0.5%; lotion 0.1%].

F. High-Potency Topical Corticosteroids

1. Betamethasone dipropionate Augmented (Diprolene) apply to affected areas bid [oint, lotion 0.05%].
2. Clobetasol (Temovate) apply to affected areas bid [cream, oint 0.05%].
3. Diflorasone (Florone) apply to affected areas qd-qid [cream, oint 0.05%].
4. Halobetasol (Ultravate) apply to affected area bid [cream, oint 0.05%]

- G. Systemic Corticosteroids** are reserved for severe, widespread reactions, or for severe involvement of the hands, face, or genitals.

1. Prednisone 1-2 mg/kg PO, tapering over 10-18 days.
2. For patients who are at risk for complications of fluid retention due to the mineralocorticoid effects of prednisone, substitute dexamethasone (Decadron), 0.75 mg/kg PO; particularly effective in older patients with cardiac problems or if taking diuretics.

- H. Antibiotic therapy** should be initiated prophylactically if there is a risk for secondary infection.

1. Erythromycin 250 mg PO bid-tid with meals.
2. Dicloxacillin (if staphylococci resistance is possible) 250 mg PO qid [250, 500 mg].

- I.** All patients with chronic forms of dermatitis should only use mild soap for cleaning, and they should lubricate the skin with lotion or petroleum jelly on a regular basis to keep the skin well hydrated.

III. Verruca Vulgaris (Common Skin Warts)

- A.** Verruca vulgaris warts are benign, usually self-regressing papilloma of the skin and adjacent mucous membranes caused by the human papilloma virus (HPV).

- B.** The peak incidence of warts occurs during the second decade of life with about 10% of teenagers having them.

- C.** Warts can occur at every location on the skin, but warts in different locations often assume different appearances:

1. Plantar or mosaic warts on the soles are hyperkeratotic.
2. Common warts on the hands have a dome shape and velvety surface.
3. Flat warts occur over the face, arms, or around the knees.
4. Anogenital warts, called condylomata acuminata, occur on the genitalia or anorectal area.
5. Buschke-Lowenstein tumor or verrucous carcinoma appears as a persistent, large wart of the foot or anogenital region that can become malignant.

D. Differential Diagnosis

1. **Molluscum contagiosum.** Shiny, dome-shaped, papilla like a wart, but has an umbilicated center.
2. **Calluses.** Can look like warts, but lack the thrombosed punctate capillaries of warts.

E. Treatment of Verruca Vulgaris

1. Cryotherapy and Chemical Agents

- a. Chemicals such as cantharidin or liquid nitrogen are favored over electrodesiccation which can scar. Cryosurgery with liquid nitrogen should freeze wart and about 1 mm of surrounding tissue.
- b. **Over-the-counter Wart Preparations.** Mediplast (for plantar use) salicylic acid plaster for home use.

- c. **Prescription Wart Preparation.** Duofilm, Occlusal, Occlusal-HP, Podofilox (Condylox), Viranol (gel), cantharidin alone or in combination (Cantharone, Cantharone Plus, Verrusol).
- d. Trans-Ver-Sal: Salicylic acid 15%, apply at night and remove the following morning.
- e. Unresponsive or diffuse warts can be treated with topical 5-fluorouracil or dinitrochlorobenzene (DNCB).

- 2. **Surgery.** Anesthetize area, and use a dermal curet to bluntly dissect the wart and completely remove. Potential for scarring, and recurrent warts may form in the scar.
- 3. Vaccines prepared from wart tissue are not advisable because of the oncogenicity of HPV.

References: See page 148.

Common Skin Diseases

I. Alopecia Areata

- A. Characterized by asymptomatic, noninflammatory, non-scarring areas of complete hair loss most commonly involving the scalp, but may involve any area of hair-bearing skin.
- B. Probably caused by auto-antibodies to hair follicles. Emotional stress is sometimes a precipitating factor. The younger the patient and the more widespread the disease, and the poorer the prognosis.
- C. Regrowth of hair after the first attack takes place in 6 months in 30% of cases, with 50% regrowing within 1 year and approximately 80% growing within 5 years. 10-30% of patients will not regrow hair; 5% progress to total hair loss.
- D. Lesions are well defined, single or multiple, round or oval areas of total hair loss. In active lesions, "exclamation point" hairs (loose hairs 3-10 mm in size with a tapered, less pigmented proximal shaft) are seen at the margins.
- E. **Differential Diagnosis:** Tinea capitis, trichotillomania, secondary syphilis, and lupus erythematosus.
- F. A VDRL or RPR test for syphilis should always be obtained. A CBC, SMAC, sedimentary rate, thyroid function tests, antinuclear antibody should be done to screen for pernicious anemia, chronic active hepatitis, thyroid disease, lupus erythematosus, and Addison's disease.
- G. **Therapy.** Topical steroids, intralesional steroids, and topical minoxidil may be somewhat effective. Hair regrowth will usually occur in 1 year without therapy.

II. Scabies

- A. Characterized by an extremely pruritic eruption usually accentuated in the groin, axillae, navel, breasts, and finger webs, with sparing the head.
- B. Scabies is spread by skin to skin contact. The diagnosis is established by finding the mite, ova, or feces in scrapings of the skin, usually of the finger webs or genitalia.
- C. Treatment of choice for nonpregnant adults and children is gamma benzene hexachloride (Kwell), applied for 8-12 hours, then washed off. CNS toxicity has been reported in infants in whom it was used too frequently.
- D. Elimite, a 5% permethrin cream, is more effective but more expensive than lindane (Kwell). With the availability of Elimite, crotamiton (Eurax) has little use in the management of scabies.
- E. Treatment should be given to all members of an infected household simultaneously. Clothing and sheets must be washed on the day of treatment. Treatment failures usually result from incomplete treatment or failure to treat all members of the household simultaneously.

III. Acne Rosacea

- A. This condition commonly presents in fair-skinned individuals and is characterized by papules, erythema and telangiectasias.

92 Common Skin Diseases

- B. Initial treatment consists of tetracycline type drugs. Once there has been some clearing, topical metronidazole gel (Metro-gel) can prevent remission. Sunblock should be used because sunlight can exacerbate acne rosacea.

II. Seborrheic Dermatitis

- A. Seborrheic dermatitis is often called cradle cap, dandruff, or seborrhea. It has a high prevalence in infancy, and then is not common until after puberty. Predilection is for the face, retroauricular region, and upper trunk.

B. Clinical Findings

1. Infants present with an adherent, waxy, even asbestos-like, laminated, scaly lesions on the scalp vertex also known as "cradle cap."
2. In adults, the eruption is bilaterally symmetrical, affecting the scalp with patchy or diffuse, dull, yellow-like erythema, and waxy yellow, greasy scaling on the forehead, retroauricular region, auditory meatus, eyebrows, cheeks and nasolabial folds.
3. Trunk areas affected include the presternal, interscapular regions, the umbilicus, intertriginous surfaces of the axilla, inframammary regions, groin, and anogenital crease.
4. Pruritus is mild. Bacterial infection is indicated by vesiculation and oozing.

C. Differential Diagnosis

1. Lupus erythematosus - has telangiectasias almost always.
2. Psoriasis - thick, micaceous white scale.
3. Tinea versicolor - fine scale, usually tan or pink; positive KOH.

D. Treatment

1. **Scalp:** Selenium sulfide or tar shampoos; sulfur and salicylic acid lotions as keratolytics; topical corticosteroid lotions.
2. **Face, neck, and intertriginous regions:** Hydrocortisone 1 or 2 ½%.
3. **Trunk:** Fluorinated steroids can be used if severe.

V. Drug Eruptions

- A. Drug eruptions, may be type I, type II, type III, or type IV immunologic reactions.
- B. Cutaneous drug reactions may start within 7 days of initiation of the drug or within 4-7 days after the offending drug has been stopped.
- C. The cutaneous lesions usually become more severe and widespread over the following several days to 1 week and then clear over the next 7-14 days.
- D. Lesions most often start first and clear first from the head and upper extremities to the trunk and lower legs. Palms, soles, and mucous membranes may be involved.
- E. Most drug reactions appear as the typical maculopapular drug reaction. Tetracycline is associated with a fixed drug eruption; thiazide diuretics have a tendency for photosensitivity eruptions.
- F. Specifically question the patient concerning medications, eye drops, nasal sprays, suppositories, immunizations, vitamins, laxatives, analgesics, and aspirin. These drugs are capable of causing cutaneous reactions.

G. Treatment of Drug Eruptions

1. Oral antihistamines are very useful. Diphenhydramine (Benadryl), 25-50 mg q4-6h.
2. Soothing, tepid water baths in Aveeno or corn starch or cool compresses are useful.
3. Drying antipruritic lotions such as Caladryl and calamine with menthol and/or phenol are sometimes helpful.
4. **Severe Signs and Symptoms.** A 2-week course of systemic steroids (prednisone starting at 60 mg per day and then tapering) will usually stop the symptoms and prevent further progression of the eruption within about 48 hours of the onset of therapy.

H. Erythema Multiforme

1. Presents as dull red macules or papules on the back of hands, palms, wrists, feet, elbows and knees. The periphery is red and the center becomes blue or darker red, hence the characteristic target or iris lesion.

2. This reaction is most commonly associated with a drug reaction, sulfa medications and phenytoin (Dilantin) being the most common agents. It is also seen as a reaction to HSV infections, mycoplasma, and Hepatitis B.
3. Erythema multiforme major or Steven's Johnson syndrome is diagnosed when mucous membrane or eye involvement is present.
4. The value of corticosteroids treatment is debated. Nonetheless, often prednisone 30-60 mg/day is given with a 2-4 week taper.
5. For HSV-driven erythema multiforme, acyclovir may be helpful, particularly when given prophylactically in cases of recurrent erythema multiforme secondary to HSV.
6. Ophthalmologic consultation is obtained for ocular involvement.

VI. Groin Rashes

- A. In adults groin rashes may be due to Candida or tinea.
- B. Candida lesions are often moist, red and confluent with peeling borders that are surrounded by satellite lesions. Candida tends to involve intertriginous areas and scrotum.
- C. Tinea clears centrally, has a sharp border with a scale, and spares the scrotum.
- D. **Treatment.** Imidazoles are effective for both tinea and Candida, but nystatin only treats Candida.
 1. Miconazole (Micatin), apply to affected area bid; cream: 2% [15, 30 gm].
 2. Clotrimazole (Lotrimin), apply to affected area bid; cream: 1% [15, 30, 45, 90 gm], lotion: 1% [30 mL].
 3. Econazole (Spectazole), apply to affected area once daily; cream: 1% [15, 30, 85 g].
 4. Ketoconazole (Nizoral), apply to affected area qd-bid; cream: 2% [15, 30, 60 gm].
 5. Oxiconazole (Oxistat), apply to affected area qd; cream: 1% [15, 30, 60 gm], lotion: 1% [30 mL].
 6. Nystatin (Mycostatin), apply to affected area bid; cream, oint: 100,000 U/gm [15, 30 gm]
- E. Allylamines (naftifine and terbinafine) are more effective against tinea, but have little activity against Candida.
 1. Naftifine (Naftin), apply to affected area bid; [cream 15, 30, 60 gm]: [gel 20, 40, 60 gm]; minimal Candida coverage.
 2. Terbinafine (Lamisil), apply to affected area bid; cream: 1% [15, 30 g]; minimal Candida coverage.

VII. Nail Infections

A. Paronychias

1. Chronic infections around the edge of the nail, paronychias, are due almost universally to Candida albicans.
2. Acute paronychia presents as tender, red, swollen areas of the nail fold, but not the nail itself. Pus may be seen through the nail plate or at the paronychial fold. In acute cases, the most common causative bacteria are staphylococci, beta-hemolytic streptococci, and gram-negative enteric bacteria.
3. Predisposing factors to paronychia include minor trauma and splinters under the nail. Moisture predispose to Candida.
4. **Diagnosis of Paronychial Lesions.** Chronic lesions are usually caused by Candida and may be diagnosed by KOH prep or by fungal culture (DTM culture). Acute lesions are usually bacterial and may be cultured for bacteria.
5. **Treatment of Chronic Candida Paronychia**
 - a. Stop all wet work and apply clotrimazole (Lotrimin) 1% solution or thymol 2-4% in chloroform tid.
 - b. Resistant cases can be treated with a 3-6 week oral course:
 - (1) Fluconazole (Diflucan), 100 mg PO daily
 - (2) Itraconazole (Sporanox) 200-400 mg PO daily.

(3) Ketoconazole (Nizoral), 200 mg PO daily

6. Treatment of Acute Bacterial Paronychia

a. Wet compresses made with Burow's solution.

b. Oral Antibiotics

(1) Dicloxacillin 500 mg PO qid.

(2) Cephalexin (Keflex) 500 mg PO qid.

(3) Cefadroxil (Duricef) 500 mg PO bid.

(4) Erythromycin 500 mg PO qid.

c. If redness and swelling do not resolve, and a pocket of pus remains, drainage is indicated.

B. Nail Plate Infections

1. Candida does not invade the nail plate.

2. Thickened, hyperkeratotic, crumbly nails are due to dermatophytes (ie, tinea unguium). Fingernails so infected may be frequently cured or significantly improved with oral treatment with griseofulvin for about 6 months. The new imidazole, itraconazole, and allylamine, terbinafine, appear to be very effective in nail infections, but at a much higher cost. Toenails are very resistant to treatment, and require oral treatment for longer than one year, with about a 50% response rate, when griseofulvin is used.

3. Terbinafine, itraconazole, or fluconazole, due to their high affinity to keratin and fungicidal properties, are the treatments of choice for onychomycosis.

4. Itraconazole (Sporanox) 200 mg qd for the first 7 days of each month for 4 months. Response rates up to 90% have been reported; expensive.

5. Terbinafine (Lamisil) 250 mg bid for 4 months; very expensive.

6. Fluconazole (Diflucan) 150 mg PO qd. (One and a half of the 100 mg tablets is more economical than the 150 mg tablet.)

7. Griseofulvin 500 mg PO daily in a single or divided dose; for fingernails 6-9 months, or for toenails 9-12 months. Patients should be followed by CBC and SMAC every 3 months.

VIII. Tinea Versicolor

A. Caused by *Malassezia furfur*, a normal skin resident.

B. **Predisposing Factors:** Pregnancy, serious underlying diseases, genetic predisposition, corticosteroid therapy.

C. Lesions may be spotty, hyper- or hypopigmented with slightly hyperkeratotic papules; the upper two-thirds of the horny layer has splits and mild scaling. Lesions favor scalp margins, upper trunk, neck and shoulders. Rarely it may involve the flexures, distal parts of the extremities, and the face.

D. A glass slide can be used to scrape the lesion, and prepare a KOH prep. Gnarled, angulated, short hyphae and clusters of spores will be visible. A negative KOH examination virtually excludes the diagnosis, unlike dermatophyte infections, where a positive KOH may be difficult to obtain.

E. Treatment

1. Selenium sulfide shampoo or lotion 2.5% qhs for 15 minutes for 7 days or

2. Topical imidazole bid for 4 weeks.

a. Miconazole Nitrate (Micatin); apply to affected areas bid; cream: 2% [15, 30 gm].

b. Clotrimazole (Lotrimin), apply to affected area bid for up to 4 wk; cream: 1% [15, 30, 45, 90 gm], lotion: 1% [30 mL]

c. Ketoconazole (Nizoral) apply to affected area(s) qd-bid; cream: 2% [15, 30, 60 gm]

3. Oral ketoconazole (Nizoral) in a single dose or for several days, 200 mg PO qd, may be useful for resistant disease. 200 mg PO daily for 2-4 weeks is advised if recurrences occur.

4. Relapses are very common. Prophylactic therapy, once weekly to monthly, with topical or oral agents should be encouraged if relapses occur.

IX. Dermatophytosis

A. Dermatophytosis is a superficial fungal infection caused by fungi belonging to the genera *Microsporum*, *Trichophyton*, or *Epidermophyton*. May be anthropophilic (transmitted from person to person) or zoophilic (transmitted by animals, especially cats).

B. Pathophysiology. Dermatophyte fungi grow only within the keratin layers of the skin, and within the hair. Hydration and occlusion of the skin (by shoes) facilitate infection.

C. Clinical Findings

- 1. Tinea Capitis.** Most often noninflammatory, presenting with scalp patches of scaling and alopecia.
- 2. Tinea Pedis.** Most commonly presents with scaling, maceration, and fissuring in the toe webs and soles.
- 3. Tinea Manuum.** Usually presents with diffuse scaling of one or, less commonly, both palms. Frequently there is fine scaling in the skin creases.
- 4. Tinea Corporis and Tinea Cruris.** Erythematous, scaly plaques occur on the trunk or other non-hairy areas or groin. The border of the lesion is exceedingly well demarcated (without satellite lesions as in *Candida*) with increased scaling or erythema, papules, or vesicles. There may be central clearing.
- 5. Tinea Unguium.** Affects the toenails more commonly than the fingernails. Subungual hyperkeratosis and a whitish or yellowish discoloration of the nail.
- Candida does not invade the nail plate.

D. Diagnostic Tests

- 1. Potassium Hydroxide Exam.** Scales are scraped from the lesion and digested with 10% KOH with gentle heating, fungal hyphae and spores may be visible.
- If potassium hydroxide exam is negative, the scales may be cultured on a fungal medium.
- Wood's lamp examination is of limited value, since the most commonly found pathogenic agents for tinea do not fluoresce.

E. Differential Diagnosis. Noninflammatory tinea capitis may be confused with seborrheic dermatitis, or secondary syphilis. Tinea cruris may be confused with intertriginous dermatitis that usually spares the crease. Tinea unguium may be confused with nail psoriasis.

F. Treatment of Tinea of the Scalp

- Ketoconazole (Nizoral) 200 mg PO daily for 6-8 weeks or topical imidazole solution bid for 6-8 weeks.
- Itraconazole (Sporanox) 100-200 mg PO qd [100 mg]
- Griseofulvin, 500 mg PO day in single or divided doses for 6-8 weeks [250, 500 mg]

G. Treatment of Tinea of the Skin Folds, Palms, and Soles

- Miconazole (Micatin); apply to affected areas bid; cream: 2% [15, 30 gm]
- Ketoconazole (Nizoral) apply to affected area qd-bid; cream: 2% [15, 30, 60 gm]
- Econazole (Spectazole) apply to affected area bid; cream: 1% [15, 30, 85 g]
- Clotrimazole (Lotrimin), apply to affected area bid for up to 4 wk; cream: 1% [15, 30, 45, 90 gm], lotion: 1% [30 mL]
- Itraconazole (Sporanox) 200 mg PO qd-bid for 1 week [100 mg]

X. Pityriasis Rosea

A. An acute inflammatory dermatitis characterized by self-limited, lesions distributed on the trunk and extremities. A viral cause is hypothesized. Most common between the ages of 10 and 35.

B. Clinical Manifestations

- The initial lesion, called the "herald patch", can appear anywhere on the body, and is 2-6 cm in size, and begins a few days to several weeks

before the generalized eruption. The hands, face, and feet are usually spared.

2. The lesions are oval, and the long axes follow the lines of cleavage. Lesions are 2 cm or less, pink, tan, or light brown. The borders of the lesions have a loose rim of scales, peeling peripherally, called the "collarette."

3. Pruritus is usually minimal. Fever and malaise are occasionally associated.

C. Differential Diagnosis. Secondary syphilis (always check VDRL for atypical rashes), drug eruptions, viral exanthems, acute papular psoriasis, tinea corporis.

D. Treatment

1. Topical antipruritic emollients (Caladryl) relieve itching. Ultraviolet therapy may be used within the first week.
2. The disease resolves in 2-14 weeks and recurrences are unusual.

References: See page 148.

Bacterial Infections of the Skin

I. Furuncles and Carbuncles

A. A furuncle, or boil, is an acute perifollicular staphylococcal abscess of the skin and subcutaneous tissue. Lesions appear as an indurated, dull, red nodule with a central purulent core, usually beginning around a hair follicle or a sebaceous gland. Furuncles occur most commonly on the nape, face, buttocks, thighs, perineum, breast, and axillae.

B. A carbuncle is a coalescence of interconnected furuncles that drain through number of points on the skin surface.

C. The most common cause of furuncles and carbuncles is coagulase-positive *S aureus*. Cultures should be obtained from all suppurative lesions.

D. Treatment of Furuncles and Carbuncles

1. Warm compresses and cleansing.
2. Dicloxacillin (Pathocil) 500 mg PO qid for 2 weeks or other penicillinase-resistant antibiotic.
3. Manipulation and surgical incision of early lesions should be avoided, because these maneuvers may cause local or systemic extension. However, when the lesions begin to suppurate and become fluctuant, drainage may be performed by "nicking" the lesion with a No. 11 blade.
4. Draining lesions should be covered with topical antibiotics and loose dressings. Placement of rubber drains or wicks may prevent healing and lead to scarring and should be avoided. A lesion typically resolves within 2 weeks.

II. Superficial Folliculitis

A. Superficial folliculitis is characterized by small dome-shaped pustules at the ostium of hair follicles; caused by coagulase-positive *S aureus*.

B. Multiple or single lesions appear on the scalp, back, and extremities. In children, the scalp is the most common site.

C. Gram stain and bacterial culture supports the diagnosis.

D. Treatment. Local cleansing and erythromycin 2% solution applied topically bid to affected areas.

III. Impetigo

A. Small superficial vesicles appear that eventually form pustules and develop a stuck-on, honey-colored crust. A halo of erythema often surrounds the lesions.

B. Impetigo contagiosa occurs most commonly on exposed surfaces such as the extremities and face, where minor trauma, insect bites, contact dermatitis, or abrasions may have occurred.

C. Gram stain of an early lesion or the base of a crust often reveals gram-positive cocci. Bacterial culture yields *S aureus*, group A beta-hemolytic

streptococci, or both.

D. Treatment of Impetigo

1. A combination of systemic and topical therapy is recommended for moderate to severe cases of impetigo for a 7- to 10-day course:
 - a. Dicloxacillin 250-500 mg PO qid; should be the initial treatment because of erythromycin-resistant strains of *S aureus*.
 - b. Erythromycin 250-500 mg PO qid
 - c. Cephalexin (Keflex) 500 mg PO qid
2. Mupirocin (Bactroban): Highly effective against all staphylococci, including methicillin-resistant *S aureus* and *Streptococcus pyogenes*. Applied bid-tid for 2-3 weeks or until 1 week after lesions heal. Bacitracin (neomycin, polymyxin B) ointment tid may also be used.

E. Complications

1. Acute glomerulonephritis is a serious complication of impetigo, with an incidence of 2-5%; most commonly seen in children under the age of 6. Treatment of impetigo does not alter the risk of acute glomerulonephritis.
2. Rheumatic fever has not been reported after impetigo.

IV. Cellulitis

- A. Cellulitis is a diffuse suppurative bacterial inflammation of the subcutaneous tissue.
- B. Localized erythema, warmth, and tenderness are characteristic. Cutaneous erythema is poorly demarcated from uninvolved skin; may be accompanied by malaise, fever, and chills.
- C. The most common causes are beta-hemolytic streptococcal and *S aureus*. Complications include gangrene, metastatic abscesses, and sepsis.

D. Treatment

1. Dicloxacillin or cephalexin provide adequate coverage for either streptococci and staphylococci. Penicillin may be added to increase activity against streptococci.
2. The affected body part should be kept elevated.
3. **Antibiotic Therapy**
 - a. Dicloxacillin (Dycil, Pathocil) 15 mg/kg per day in 4 divided doses for 7-12 days; adults: 500 mg qid
 - b. Cephalexin (Keflex) 50 mg/kg per day PO in 4 divided doses for 7-10 days; adults: 500 mg PO qid
 - c. Azithromycin (Zithromax) 500 mg on day 1, then 250 mg PO qd for 4 days
 - d. Erythromycin ethylsuccinate 30-40 mg/kg per day in 3 divided doses for 7-10 days; adults: 250-500 mg qid
 - e. Amoxicillin/clavulanate (Augmentin) 500 mg PO tid for 7-10 days
 - f. Mupirocin (Bactroban) ointment apply topically to affected areas bid.

References: See page 148.

Psoriasis

I. Clinical Presentation

- A. Psoriasis is a chronic skin disease characterized by epidermal hyperplasia and an accelerated rate of epidermal turnover. Psoriasis is a lifelong disorder that may consist of only a few patches on the scalp, elbows or knees, or it may be extensive with total skin involvement.
- B. It has an unpredictable course with improvement or exacerbation of lesions. Onset occurs at any age with equal frequency in males and females. The mean onset of age is 27.8, with 35% having an onset before 20 years.
- C. The lesion is elevated and erythematous with thick, micaceous, silver, loosely adherent scales cover the lesion.
 1. Scraping off the scale leaves a bleeding point (Auspitz sign).

2. Lesion predilection is for the sacral region, over extensor surfaces (elbows, knees, lumbosacral), and scalp. The appearance of disease is often associated with superficial cutaneous trauma (Koebner phenomenon).
 3. Mucosal psoriasis consist of circinate, ring-shaped, whitish lesions on the tongue, palate, or buccal mucosa.
- D. Onycholysis, or separation of the nail plate from the underlying nail bed is frequently seen, as well as a yellow-brown discoloration underneath the nail, known as an "oil spot."
- E. **Aggravating Factors.** Stress, infection, certain drugs (lithium and some beta-blockers).
- F. 5-10% of the patients have an associated arthritis characterized by asymmetrical distal oligoarthritis involving small joints; a smaller number of patients have a rheumatoid arthritis-like picture involving symmetrical larger joints or a spondyloarthropathy. The arthritis may be mutilating and very destructive.

II. Treatment of Psoriasis

A. Topical corticosteroids

1. Hydrocortisone 1 to 2.5% on face, neck, axilla, groin, intertriginous regions.
2. Fluorinated corticosteroids in plaque regions.
3. Occlusive dressings can be used to flatten out psoriatic lesions. Intralesional steroids are also useful.
4. **Scalp psoriasis.** Remove scales with warm oil before shampooing with tar. Topical corticosteroid lotion can be massaged into the scalp.
5. **Nail psoriasis.** Apply topical corticosteroids to the nail under occlusion 2-3 times weekly.

B. Medium Potency Agents

1. Betamethasone valerate (Valisone) apply qd-bid [cream, oint, 0.1%].
2. Fluocinolone acetonide (Synalar) apply bid-qid [cream 0.025, 0.2%; oint 0.025%].

C. High Potency Agents

1. Betamethasone dipropionate augmented (Diprolene) apply to affected areas qd-bid [gel, oint, 0.05%].
2. Clobetasol (Temovate) apply to affected areas bid [cream, oint 0.05%].
3. Flurandrenolide (Cordran) apply bid-tid [oint, cream 0.05%].
4. Halcinonide (Halog) apply bid-tid [cream 0.025, 0.1%; oint 0.1%].
5. Betamethasone dipropionate apply qd-bid [oint, cream, 0.05%].
6. Amcinonide (Cyclocort) apply bid-tid [cream, oint 0.1%].

D. Vitamin D Analog

1. Calcipotriene (Dovonex) 0.005% ointment, apply a thin layer to affected skin bid [30, 60, 100 g].

E. Systemic Agents. Indicated for severe, extensive psoriasis.

1. Etretinate (Tegison) 0.75 mg/kg/day in divided doses PO [caps: 10, 25 mg]; contraindicated in women who may ever become pregnant.
2. Methotrexate 2.5 mg PO at 12 hour intervals for 3 doses or 10-25 mg/week; liver toxicity is a major problem.

F. UV Light. Effective for widespread psoriatic lesions; however, overexposure can exacerbate the disease.

References: See page 148.

Pruritus Ani

Pruritus ani is a symptom complex consisting of perianal discomfort and itching. It is much more common in men than women, and it is idiopathic in 50-90%.

I. Clinical Evaluation

- A.** Discomfort is exacerbated by friction or a warm, moist perineal environment. Poor anal hygiene or over-cleansing with soap is often a contributing factor. Diabetes, antibiotic use, vaginal or rectal discharge or infection, and other skin disorders should be excluded.
- B.** Patients with idiopathic pruritus often have intermittent seepage from the anal canal.
- C.** A decrease in resting anal canal pressure occurs with coffee intake, and exacerbation of symptoms can occur with ingestion of caffeine.

D. Common Conditions Causing Pruritus Ani

- 1. Anorectal Disease.** Fissures, fistula-in-ano, proctitis, prolapsing hemorrhoids, skin tags, sphincter dysfunction
 - 2. Infection.** Candida organisms, condyloma acuminata, pinworms, scabies
 - 3. Dermatologic Disorders.** Contact dermatitis, lichen planus, lichen sclerosus, psoriasis, seborrhea.
- E. Physical Exam.** Mild pruritus ani manifests as mild erythema and excoriations of the perianal skin. In later stages, the skin may be raw, red, and oozing or pale and lichenified with exaggerated skin folds. Examination of the anus and rectum may reveal hemorrhoids, fissures, or decreased resting anal tone.

F. Treatment of Pruritus Ani

- 1.** Treatment of idiopathic pruritus ani is nonspecific and is aimed at restoring clean dry intact perianal skin.
- 2.** The perineum should be gently cleansed after bowel movements. Premoistened wipes may be used, but those containing alcohol or witch hazel will irritate the perianal skin.
- 3.** Drying should also be done gently, preferably with a hair dryer.
- 4.** The area dry may be kept dry with absorbent cotton tucked into the anal cleft.
- 5.** Caffeinated beverages or any other dietary items that seem to exacerbate symptoms should be avoided.
- 6.** Use of any of the perianal lotions and ointments is not mandatory and may exacerbate the problem by producing atrophy of the skin or allergic reactions.

References: See page 148.

Gynecologic Disorders

Management of the Abnormal Pap Smear

I. Screening for Cervical Cancer

- A. The American Cancer Society currently recommends annual Pap smears for women who are sexually active or who have reached the age of 18.
- B. After three consecutive satisfactory, normal smears, testing may be performed less frequently, but it should be performed at least every 2-3 years. If a woman has had SIL on any previous Pap smear, annual smears should be performed throughout her life.

II. Management of Minor Pap Smear Abnormalities

A. Satisfactory, but Limited by Few (or absent) Endocervical Cells

1. Endocervical cells are absent in up to 10% of Pap smears premenopause and up to 50% postmenopausally.
2. **Management.** Either repeat Pap annually or only recall women with previously abnormal Pap smears.

B. Unsatisfactory for Evaluation

1. Repeat Pap smear midcycle in 6-12 weeks.
2. If atrophic smear, treat with estrogen cream for 6-8 weeks, then repeat Pap smear.

C. Benign Cellular Changes

1. Infection-Candida

- a. Most cases represent asymptomatic colonization.
- b. Treatment is offered for symptomatic cases. Repeat Pap at usual interval.

2. Infection-Trichomonas.

If wet preparation is positive, treat with metronidazole (Flagyl), then continue annual Pap smears.

3. Infection-Predominance of Coccobacilli consistent with Shift in Vaginal Flora

- a. This finding implies possible bacterial vaginosis, but is non-specific.
- b. Diagnosis should be confirmed by findings of a homogeneous vaginal discharge, positive amine test, and clue cells on microscopic saline suspension.

4. Infection-Herpes Simplex Virus

- a. Pap smear has poor sensitivity but good specificity for HSV; a positive smear usually is caused by asymptomatic infection.
- b. Inform patient of pregnancy risks and possibility of transmission.
- c. No treatment is necessary. Repeat Pap as for a benign result.

5. Inflammation on Pap Smear

- a. Mild inflammation on an otherwise normal smear does not need further evaluation.
- b. **Moderate or severe inflammation** should be evaluated with a saline preparation, KOH preparation, and gonorrhea and Chlamydia test. If the source of infection is found, treatment should be provided, and repeat Pap smear is done every 6 to 12 months. If no etiology is found, a repeat Pap smear in 6 months.
- c. Infrequently, inflammation may be the only manifestation of high-grade squamous intraepithelial lesions (HGSIL) or even invasive cancer; therefore, persistent inflammation is an indication for colposcopy.

6. Atrophy with Inflammation

- a. Common in post-menopausal women or in those with estrogen-deficiency states.
- b. Atrophy may be treated with vaginal estrogen for 4-6 weeks, then repeat Pap smear.

7. Hyperkeratosis and Parakeratosis

- a. Parakeratosis is defined as dense nuclei within a keratin layer. When no nuclei are present, the cells are designated hyperkeratotic.
- b. Parakeratosis and hyperkeratosis occur as a reactive mechanism to physical, chemical, or inflammatory trauma, and it may clinically appear as leukoplakia. Benign-appearing parakeratosis or hyperkeratosis requires only a repeat Pap test in 6 months. When the finding persists, colposcopy is indicated.

III. Management of Squamous Cell Abnormalities**A. Atypical Squamous Cells of Undetermined Significance (ASCUS)**

1. Indicates cells with nuclear atypia, but not due to human papilloma virus (HPV).
2. A Pap smear should be obtained every 6 months for 2 years. Annual Pap smears may be instituted after 3 consecutive satisfactory, negative smears. A repeat ASCUS smear within 2-years requires colposcopic evaluation.
3. ASCUS associated with severe inflammation and an identifiable cause of infection can be managed by treating the infection and re-evaluating the patient in 4-6 months with a repeat Pap smear. If ASCUS persists, colposcopy should be performed.
4. ASCUS in a postmenopausal patient may be secondary to vaginal atrophy. The patient should be treated with intravaginal estrogen cream for four weeks (even if the patient is receiving oral estrogen), followed by a repeat Pap smear. Colposcopy should be performed if ASCUS persists.
5. ASCUS with a qualification favoring a neoplastic process (SIL) should be evaluated with colposcopy.
6. ASCUS in a noncompliant patient or in a patient with a history of SIL on a previous Pap smear should be evaluated with colposcopy.

B. Low-Grade Squamous Intraepithelial Lesions (LSIL)

1. LSIL includes HPV and CIN 1 (or mild dysplasia). Koilocytotic atypia is indicative of HPV.
2. Pap smear should be repeated every 6 months for 2 years. If 3 consecutive Pap smears are negative, annual Pap smears can then be performed. If LSIL recurs on a subsequent smear within 2 years, or if subsequent smears reveal a high-grade squamous intraepithelial lesion (HGSIL), the patient should receive colposcopic evaluation.
3. LSIL has a high spontaneous resolution rate, so expectant management is reasonable; however, approximately 20% of patients with LSIL will be found to have CIN 2 or 3 on biopsy.
4. LSIL, alternatively, may be followed-up with immediate colposcopy, endocervical curettage, and directed biopsy.

C. High-Grade Squamous Intraepithelial Lesion (HGSIL; moderate/severe dysplasia; CIN 2, CIN 3, carcinoma in situ). These findings must be evaluated by colposcopy and directed biopsy.**IV. Management of Glandular Cell Abnormalities****A. Endometrial Cells on Pap Smear**

1. When a Pap smear is performed during menstruation, endometrial cells may be present. However, endometrial cells on a Pap smear performed during the second half of the menstrual cycle or in a post-menopausal patient may indicate polyps, hyperplasia, or endometrial adenocarcinoma.
2. An endometrial biopsy should be considered in these women.

B. Atypical Glandular Cells of Undetermined Significance (AGUS)

1. A colposcopic examination, repeat Pap smear, and endocervical sampling should be performed.
2. If the cells are of endometrial origin, an endometrial biopsy, a fractional D&C, or a diagnostic hysteroscopy should be performed.

C. Adenocarcinoma. This diagnosis requires evaluation that may include endocervical curettage, cone biopsy, and/or endometrial biopsy.

V. Colposcopically Directed Biopsy

A. Liberally apply a solution of acetic acid 3-5% to cervix, and inspect cervix for abnormal areas (white epithelium, punctation, mosaic cells, atypical vessels). Obtain biopsies of any abnormal areas under colposcopic visualization. Record location of each biopsy.

B. Monsel solution may be applied to stop bleeding.

C. Endocervical Curettage is done routinely during colposcopy, except during pregnancy.

VI. Treatment Based on Biopsy Findings

A. Benign Cellular Changes (infection, reactive inflammation). Treat infection. Repeat smear every 4-6 months; after 2 negatives, repeat yearly.

B. Treatment of Squamous Intraepithelial Lesions

1. Condyloma Acuminata. Use either cryotherapy or electrosurgical loop excision.

2. Low Grade Squamous Intraepithelial Lesions (LSIL)

a. Conservative Approach. Since the risk of progression is at most 20% and the lesion is not dangerous until it progresses, these lesions may be followed with repeat Pap smear at 4-6 month intervals until there is evidence of progression to HGSIL or persistence of low grade SIL.

b. If the untreated lesion does not resolve after a year, reevaluation by colposcopy, biopsy, and ablation are indicated.

3. High Grade Squamous Intraepithelial Lesion (or treated LSIL)

a. Ablative therapy is completed to destroy the entire transformation zone.

b. Ablation is appropriate if the entire lesion and transformation zone are seen and endocervical curettage is negative. After ablation, Pap smears are scheduled at 3-month intervals for 1 year.

C. Electrosurgical Loop Excision (LEEP) is used by 85% of gynecologists for cervical ablation because it is more effective than cryotherapy, fast, and well tolerated.

D. Cryotherapy Double Freeze Technique

1. Freeze with a lubricated liquid nitrogen probe for 3 minutes, followed by a 4-5 minute pause, repeat freeze for 3 min.

2. The entire lesion should be frozen, and a 3 mm margin of freeze should be visualized.

E. Cone Biopsy is indicated for patients with an unsatisfactory colposcopy or positive endocervical curettage.

References: See page 148.

Contraception

I. Oral Contraceptives

A. Monophasic OCs contain a constant dose of estrogen and progestin. Phasic OCs alter the dose of the progestin and (in some formulations) the estrogen component with the aim of reducing metabolic effects.

B. Progestins include norethindrone, levonorgestrel, norgestrel, norethindrone, and ethynodiol. Two new, less androgenic progestins are norgestimate and desogestrel.

C. OCs can be used safely until menopause by women who do not have any medical contraindications and who are nonsmokers.

D. Smoking with OC use increases the risk of myocardial infarction, stroke, and thromboembolic disease, particularly among women older than 35.

E. Contraindications to Oral Contraceptives

1. Carcinoma of the endometrium or other known or suspected estrogen-

dependent neoplasia

2. Cerebrovascular or coronary artery disease
3. Cholestatic jaundice of pregnancy or jaundice with prior pill use
4. Heavy cigarette smoking (>15 cigarettes per day) in women older than 35
5. Hepatic adenomas or carcinomas
6. History of deep vein thrombophlebitis or thromboembolic disorders
7. Known or suspected carcinoma of the breast
8. Known or suspected pregnancy
9. Undiagnosed abnormal genital bleeding

F. Administration of Oral Contraceptives

1. **Most younger patients** can be started on Triphasil-28, LoEstrin 1.5/30, Ortho-Novum 7/7/7, Ortho-Cept, Desogen, Ortho-Cyclen, or Ortho Tri-Cyclen.

2. Patient Instructions

- a. Begin pill on first Sunday after period starts.
- b. If missed pill, take forgotten pill as soon as remembered and take next pill as scheduled.
- c. If 2 missed pills, take 2 pills per day for 2 days, and use backup method for that month.
- d. If 3 missed pills, discontinue the pills and allow withdrawal bleed; resume after 1 week with new pack.

G. Breakthrough Bleeding

does not pose a health threat, but it is the most frequent complaint among OC users. Breakthrough bleeding becomes much less common after 3 months, and it may be caused by missing pills.

1. If bleeding is occurring early in cycle, change to a lower progesterone (Brevicon, Ovcon 35, Ortho Novum 1/50). If bleeding occurs late in cycle, change to lower estrogen (LoOvral, LoEstrin 1/20).
2. If the BTB is prolonged, regardless of where it occurs in the cycle, estrogen (Premarin) 1.25 mg, given daily for a week when the bleeding is present, will reduce bleeding.

H. Acne and Hirsutism.

Desogen, Ortho-Cept, Demulen, Ortho-Cyclen, Modicon, Ovcon-35, and Brevicon are useful because they are less androgenic.

I. Weight Gain.

Ortho-Cept, Desogen, Ortho-Cyclen, Triphasil, Ortho-Novum 7/7/7 or Jenest 28 may cause less weight gain because they are less androgenic.

J. Headache.

Some women experience headaches that usually subside after the first 3 cycles. If headaches persist after 3 months, switching to LoEstrin 1/20, LoEstrin 1.5/30, Ortho-Cept, or Desogen may be useful.

K. Nausea

is a common problem. The severity usually declines over the first several months of OC use. Taking the pill at bedtime with food often provides relief. If nausea persists, a preparation with lower progesterone may reduce nausea (Brevicon, Ovcon 35, Modicon).

L. Amenorrhea

1. Amenorrhea may occur with long-term OC users. Although not medically harmful, pregnancy testing and reassurance may be necessary.
2. If the patient continues to be bothered by the amenorrhea, oral estrogen 1.25 mg, taken with each of the 21 active OC tablets, often will restore withdrawal bleeding. Alternatively, another low-dose combination OC can be prescribed.

M. Hypertension

1. OCs can cause an increase in blood pressure in some women and it should be monitored annually.
2. Lower progesterone pills (Brevicon, Ovcon 35, Modicon) should be used; the OCP is discontinued if hypertension does not resolve.

N. Other Common Problems

1. **Ovarian Cysts.** Use a monophasic preparation instead of lower dose

triphasic preparations.

2. **Breast Tenderness.** Decrease the progesterone component (Brevicon, Ovcon 35, Modicon).
3. **Fibrocystic Breast Changes.** A pill with lower estrogen should be used (LoEstrin, Lo/Ovral, Ortho-Cept).

II. Injectable Depot Medroxyprogesterone Acetate (DMPA)

- A. DMPA acts by inhibiting ovulation; efficacy is extremely high.
- B. DMPA is given every 3 months, and it should be initiated within 5 days of the onset of menses, otherwise a back-up method is necessary for the first 2 weeks. This approach ensures that the patient is not pregnant and prevents ovulation during the first month of use.
- C. After a 150-mg injection of DMPA, ovulation does not occur for at least 3 months and 2 weeks. Therefore, a 2-week grace period exists for women receiving injections every 3 months. For women more than 2 weeks late for their injection, pregnancy should be excluded before giving the injection.
- D. Return of fertility will be delayed following discontinuation in 50% of women for up to 10 months after the last injection. Women who want to become pregnant within the next 1 or 2 years should not use DMPA.
- E. **Side Effects**
 1. Episodes of irregular bleeding and spotting are common during the first months of use. With increasing duration of use, these episodes diminish, and amenorrhea becomes common. Half of women using DMPA for 1 year have amenorrhea.
 2. Bleeding may be reduced by a short course of oral estrogen (Premarin), 1.25 mg administered daily for 7 days. A second option is a trial of a non-steroidal anti-inflammatory agent, which sometimes diminishes flow.
 3. Headaches, bloating of the abdomen or breasts, mood changes, and weight gain occur often.
- F. **Benefits**
 1. The tendency of DMPA to cause amenorrhea can make it useful for women with menorrhagia, dysmenorrhea, or iron deficiency anemia.
 2. Some women choose DMPA because its use can be concealed from the her partner.

III. Contraceptive Implants

- A. Norplant VI (levonorgestrel) implants consist of six, 34 x 2.4 mm, soft plastic implants. Effectiveness lasts 5 years.
- B. The Norplant II system consists of two implants, and it is effective for 3 years.
- C. These systems provide a long-acting, reversible, progestin-only method of contraception.
- D. Insertion of implants within 7 days of the onset of menses ensures that the patient is not pregnant and results in immediate contraception. Insertion can be performed at any time during the menstrual cycle as long as pregnancy can be ruled out.
- E. Because there is no demonstrated increased risk in thromboembolic phenomena, the implants and injectables, can all be used immediately post-partum, and they do not have an adverse effect on breast feeding.
- F. **Side Effects**
 1. Most women experience irregular bleeding during the first year; this proportion declines to one third by the fifth year.
 2. One third of women experience regular cycles. 5-10% of women experience amenorrhea.
 3. Estrogen supplementation can be given to implant users troubled by irregular bleeding. Women who experience regular cycles are of higher risk of pregnancy than those with irregular bleeding or amenorrhea. Pregnancy testing is indicated should menses cease.
 4. Some women using implants develop ovarian cysts. Although such cysts may cause lower abdominal discomfort, more often they are

asymptomatic and noted incidentally during pelvic examination. These cysts usually resolve spontaneously and are managed expectantly. Women who have experienced problematic ovarian cysts in the past, may be happier with methods that effectively suppress ovulation (combined OCP's and Depo-Provera).

5. Other side effects include weight gain, acne, headache, depression, anxiety, mastalgia, and galactorrhea.

IV. Intrauterine Devices

A. The IUD is the number one temporary contraception method used worldwide. IUD users report being more satisfied with their choice of method than users of other contraceptives.

B. An increased risk of infection with the modern IUD is related only to the insertion. IUDs do not increase the risk of ectopic pregnancy.

C. Mechanism of Action

1. IUDs-create an intrauterine environment that is spermicidal by provoking an inflammatory reaction which is toxic to sperm and to implantation. The IUD is not considered an abortifacient.
2. Progestin-releasing IUDs also thicken cervical mucus.

D. Progestasert

1. T-shaped IUD composed of a vertical stem that holds 38 mg of progesterone.
2. This IUD must be replaced at yearly intervals (effective for 18 months).

E. T Cu 380A (ParaGard). A T-shaped frame holding 380 mg of copper. The use period is 10 years.

F. Contraindications to IUD Use

1. Active, recent or recurrent pelvic inflammatory disease
2. Known or suspected gonorrhea or Chlamydia
3. Known or suspected pregnancy
4. Undiagnosed irregular or abnormal genital bleeding
5. Cervical or uterine malignancy (including unresolved PAP smear abnormalities)

G. Relative Contraindications to IUD Use

1. Increased risks for PID (frequent partners, impaired immunity)
2. HIV infection or risk factors
3. Increased risk for endocarditis
4. History of ectopic pregnancy
5. Impaired coagulation (thrombocytopenia, warfarin therapy)
6. Previous IUD expulsion or failure
7. Anemia (hematocrit <28%)
8. History of impaired fertility in a woman desiring pregnancy

V. Postcoital Contraception

A. Hormonal Postcoital Contraception

1. Ovral, two pills (estradiol 50 mcg and norgestrel 0.5 mg) are taken within 72 hours of unprotected intercourse and repeated 12 hours later; this regimen significantly reduces the pregnancy rate and is safe.
2. Low dose pills may also be used, including Lo/Ovral, Nordette, Leven, Triphasil, or Tri-Leven (yellow pills only): Take four pills, then repeat four pills 12 hours later.
3. Metoclopramide (Reglan) 10 mg, with each hormone dose, is prescribed to reduce nausea and vomiting.
4. If menstruation does not begin when expected, a pregnancy test is appropriate.

B. RU486 (Mifepristone)

1. RU486 is an abortifacient, which is a competitive inhibitor of progesterone. The drug is most effective when taken early in pregnancy.
2. Dosage is 600 mg (three 200 mg tablets). The addition of misoprostol (Cytotec) 400 mg PO, 35-48 hours after RU 486, increases efficacy to 90-100%.
3. Patient management consists of a pretreatment pregnancy test, vaginal

ultrasound for gestational age, hematocrit, and Rh type.

4. Confirmation that pregnancy has ended requires a repeat pregnancy test or vaginal ultrasound.

References: See page 148.

Endometriosis

I. Pathophysiology

- A. Ten percent of women will develop endometriosis characterized by the presence of endometrial tissue at sites outside the uterine cavity. The ectopic endometrial cells cause the cyclical dysmenorrhea of endometriosis.
- B. The most common sites are the ovaries, posterior cul-de-sac, uterosacral ligaments, posterior broad ligament, and anterior cul-de-sac. The uterine serosa, rectovaginal septum, cervix, vagina rectosigmoid, and bladder are less frequent locations.

II. Clinical Manifestations

- A. Endometriosis is characterized by cyclical pain, usually beginning prior to menses. Deep dyspareunia and sacral backache with menses are common.
- B. Infertility is a frequent consequence of endometriosis. Premenstrual tenesmus or diarrhea may indicate rectosigmoid endometriosis. Cyclic dysuria or hematuria may indicate bladder endometriosis.

III. Diagnosis

- A. Tender nodules are often palpable through the posterior vaginal fornix on bimanual examination and along the uterosacral ligaments on rectovaginal examination. Ovarian enlargement, fixation of the adnexal structures, and uterine retrodisplacement may also be detected.
- B. Ultrasound may identify adnexal masses.
- C. Endometriosis can be definitively diagnosed only by laparoscopy.

IV. Treatment of Endometriosis

- A. Initial therapy consists of a nonsteroidal anti-inflammatory drug.
 1. Naproxen (Naprosyn) 500 mg followed by 250 mg PO q6-8h prn [250, 375, 500 mg].
 2. Naproxen sodium (Aleve OTC) 200 mg PO tid.
 3. Naproxen sodium (Anaprox) 550 mg, followed by 275 mg PO tid-qid prn.
 4. Ibuprofen (Motrin) 800 mg, then 400 mg PO q4-6h prn.
 5. Mefenamic acid (Ponstel) 500 mg PO followed by 250 mg q6h prn.
- B. **Combined Estrogen-Progestin.** Low-dose, combination, monophasic birth control pills often relieve mild to moderate pelvic pain; they are often taken continuously.
- C. **Progestin-Only Regimen.** Medroxyprogesterone (Provera), 10-30 mg/d, produces significant pain relief; however, frequent breakthrough bleeding limits usefulness. Depo-Provera may be used, unless fertility is desired in the near future.
- D. **Gonadotropin-Releasing Hormone Agonists**
 1. GnRH agonists inhibit gonadal function, resulting in hypoestrogenism. Pain is relieved in most patients by the second or third month.
 2. Intramuscular leuprolide 3.75 mg once monthly, or nafarelin, 200 mg nasal spray twice daily for 3-6 months, may be used.
 3. Side effects, such as osteoporosis, hot flashes, headaches, and depression, are common. Symptoms recur after discontinuation of therapy in most patients.
- E. **Conservative Surgical Therapy.** Endometriosis is usually treated surgically at the time of diagnosis by laparoscopic cautery.
- F. **Definitive Surgery.** Hysterectomy with bilateral oophorectomy is the

definitive treatment for endometriosis.

References: See page 148.

Premenstrual Syndrome

Premenstrual Syndrome (PMS) is a cyclic disorder characterized by behavioral, emotional, and physical symptoms during the luteal phase of the menstrual cycle (the 5-11 days before menses). Emotional manifestations include irritability, depression, hostility, and social withdrawal. Physical complaints include bloating, breast tenderness, myalgia, headache, and fatigue.

I. Clinical Evaluation of Premenstrual Syndrome

- A.** PMS only occurs during ovulatory cycles. Ovulatory cycles are characterized by a regular intermenstrual interval with a consistent menstrual flow.
- B. Emotional/Behavioral Symptoms.** Anxiety, altered libido, anger, depression, food cravings, insomnia, irritability, panic attacks, poor concentration, reduced coping skills, tearfulness.
- C. Physical Symptoms.** Abdominal bloating, breast swelling or tenderness, constipation, dizziness, fatigue, fluid retention, headaches, hot flashes, and muscle aches and pains.
- D. Physical Examination.** Coexisting medical disorders or evidence of hypertension, hirsutism, or striae should be identified.
- E. Laboratory Evaluation**
 1. No specific laboratory test for PMS exist.
 2. **Testing to Identify Clinically Suspected Disorders**
 - a. Gonococcal and chlamydia culture, HIV antibody (if risk factors).
 - b. Serum prolactin level (if galactorrhea or irregular menstrual cycles or atypical mastalgia).
 - c. Measure FSH and LH levels if over 40 years of age, or if hot flashes or irregular menses.
 - d. Thyroid-stimulating hormone and complete blood count are checked if menorrhagia or chronic fatigue are present.

II. Treatment of Premenstrual Syndrome

- A. Diet and Exercise**
 1. Encourage well-balanced meals that are low in sodium and fat, and high in fiber. Simple carbohydrates and caffeine are limited.
 2. Exercise and relaxation therapy with deep breathing and mental imagery will often bring improvement.
- B.** If the patient is taking oral contraceptives, they should be discontinued during the initial phases of treatment.
- C. Fluid Retention Symptoms**
 1. Bloating, weight gain, and swelling may respond to reduced dietary salt.
 2. Diuretics may be prescribed for women with premenstrual weight gain. Start diuretic just before the onset of water retention and weight gain, and continue until the onset of menstruation.
 3. Furosemide (Lasix) 20-40 mg qAM, or any other diuretic may be used. If hypokalemia is a concern, a potassium-sparing agent, such as spironolactone 25-50 mg bid is used.
- D. Premenstrual Headache and Cramps**
 1. NSAIDs are effective for pain, particularly premenstrual migraine. Start 1 or 2 days before anticipated onset of symptoms and continue throughout menstruation.
 2. Mefenamic acid (Ponstel) 250-500 mg tid.
 3. Naproxen (Naprosyn) 250-500 mg PO bid.
 4. Naproxen sodium (Aleve, Anaprox) 550 mg bid.

E. Mastalgia

1. A support bra, reduced caffeine intake, NSAIDs and/or oral contraceptives are often helpful.
2. Bromocriptine (Parlodel), 5 mg per day, on days 10-26 of the menstrual cycle is effective.

F. Emotional Symptoms. Fluoxetine (Prozac), 20 mg/d is effective.**G. Anxiety and Agitation**

1. Alprazolam (Xanax) significantly reduces mood swings, irritability, and anxiety; 0.125-0.25 mg tid; begin several days before symptoms are due to appear and taper the dosage at the onset of menses.
2. Buspirone (BuSpar) is a nonsedating, non-benzodiazepine anxiolytic; 10 mg tid. It does not promote physical dependence, and it is useful when given cyclically in the luteal phase or continuously.

H. Ovulation Suppression

1. Oral contraceptives decrease dysmenorrhea, minimal symptoms, and emotional changes. A monophasic pill with a relatively high progestin content is recommended.
2. Danazol may be effective in PMS, but its role remains limited because of androgenic and hypoestrogenic side effects.

3. Gonadotropin-releasing Hormone (Gn-RH) Agonists

- a. Gn-RH agonists improve symptoms in patients who fail to respond to other therapies. Gn-RH agonists inhibit gonadotropin release and induces a pseudomenopause; available in nasal spray.
- b. Osteoporosis and coronary artery disease are adverse effects; the duration of therapy is limited to 3 to 6 months.

4. Estrogen

- a. Oral estrogen or transdermal estradiol may be used to treat vasomotor flushes.
- b. Medroxyprogesterone prevents development of endometrial hyperplasia.

References: See page 148.

Amenorrhea

Amenorrhea may be associated with infertility, endometrial hyperplasia, or osteopenia. It may be the presenting sign of an underlying metabolic, endocrine, congenital, or gynecologic disorder.

I. Pathophysiology of Amenorrhea

- A. Amenorrhea may be caused by either failure of the hypothalamic-pituitary-gonadal axis, or by absence of end organs, or by obstruction of the outflow tract.
- B. **Menses** usually occur at intervals of 28 ± 3 days, with a normal range of 18-40 days.
- C. **Amenorrhea** is defined as the absence of menstruation for 3 or more months in a women with past menses (secondary amenorrhea) or the absence of menarche by age 16 in girls who have never menstruated (primary amenorrhea).
- D. **Pregnancy** is the most common cause of amenorrhea.

II. Clinical Evaluation of Amenorrhea**A. History**

1. Assess the menstrual history (age of menarche, last menstrual period, previous menstrual pattern). Assess diet, medications or drugs, and psychologic stress.
2. Galactorrhea, previous radiation therapy, chemotherapy, or recent weight gain or loss may provide important clues.
3. Prolonged, intense exercise can lead to amenorrhea, and it is often

110 Amenorrhea

associated with disordered eating.

- 4. Previous pelvic surgery or evidence of increased androgen (acne, hirsutism, temporal balding, deepening of the voice, increased muscle mass, decreased breast size) should be sought.
- 5. Symptoms of decreased estrogen include hot flushes and night sweats.

Drugs Associated with Amenorrhea

Drugs that Increase Prolactin	Antipsychotics Tricyclic antidepressants Calcium channel blockers
Drugs with Estrogenic Activity	Digoxin, marijuana, oral contraceptives
Drugs with Ovarian Toxicity	Chemotherapeutic agents

B. Physical Examination

- 1. Breast development and pubic hair distribution should be assessed because they are indicators of exposure to estrogens and sexual maturity. Galactorrhea is a sign of hyperprolactinemia.
- 2. The thyroid is palpated for enlargement and nodules. Abdominal striae in a nulliparous woman may indicate hypercortisolism (Cushing's syndrome).
- 3. Hair distribution may reveal signs of androgen excess. The absence of both axillary and pubic hair in a phenotypically normal female suggests complete androgen insensitivity.
- 4. The external genitalia and vagina should be inspected for atrophy from estrogen deficiency or clitoromegaly from androgen excess. An imperforate hymen or vaginal septum can cause blockage of the outflow tract.
- 5. Palpation of the uterus and ovaries assures their presence and detects gross abnormalities.

III. Diagnostic Approach to Amenorrhea

- A. Patients 14 years of age or older with primary amenorrhea and lack of development of secondary sexual characteristics should be evaluated for congenital abnormalities.
- B. Menstrual flow requires an intact hypothalamic-pituitary-ovarian axis, a hormonally responsive uterus, and an intact outflow tract. The evaluation strategy localizes the abnormality to either the uterus, ovary, anterior pituitary, or hypothalamus.
- C. **Step One--Exclude Pregnancy.** Pregnancy is the most common cause of secondary amenorrhea and must be excluded with a pregnancy test.

D. Step Two--Exclude Hyperthyroidism and Hyperprolactinemia

- 1. Hypothyroidism and hyperprolactinemia can cause amenorrhea, and they can be excluded with a serum thyroid-stimulating hormone (TSH) and prolactin.
- 2. **Hyperprolactinemia**
 - a. Prolactin inhibits the secretion of gonadotropin-releasing hormone. One-third of women with no obvious cause of amenorrhea have hyperprolactinemia.
 - b. If the basal prolactin level is elevated, review the patient's medications, and repeat the test with the patient in a relaxed, fasting state because prolactin levels may be increased by stress, exercise, anxiety, sleep, and food ingestion.
 - c. Women with hyperprolactinemia should undergo MRI to rule out a pituitary tumor.

E. Step Three--Assess Estrogen Status

- 1. The **progesterone challenge test** is used to determine estrogen status and determine the competence of the uterine outflow tract.

2. Medroxyprogesterone (Provera) 10 mg is given orally qd for 10 consecutive days. Any uterine bleeding within 2-7 days after completion is considered a positive test. A positive result suggests chronic anovulation, rather than hypothalamic-pituitary insufficiency or ovarian failure, and a positive test confirms the presence of a competent outflow tract.
3. A negative test indicates either an incompetent outflow tract, nonreactive endometrium, or inadequate estrogen stimulation.
 - a. To rule out an abnormality of the outflow tract, a regimen of conjugated estrogens (Premarin), 1.25 mg daily on days 1 through 21 of the cycle, is prescribed.
 - (1) Medroxyprogesterone (Provera), 5 to 10 mg, is then given on the last 5 days of the 21-day cycle. (A combination oral contraceptive agent can also be used instead of the estrogen/progesterone regimen.)
 - (2) Withdrawal bleeding within 2-7 days of the last dose of progesterone confirms the presence of an unobstructed outflow tract and a normal endometrium, and the problem is localized to the hypothalamic-pituitary axis or ovaries.
4. In patients who have had prolonged amenorrhea, an endometrial biopsy should be considered before withdrawal bleeding is induced. Biopsy can reveal endometrial hyperplasia or precancerous precursors, in addition to assessing ovulatory status.

F. Step Four--Evaluation of Hypoestrogenic Women

1. This step is appropriate for women with hypoestrogenic amenorrhea, as indicated by a negative progesterone withdrawal test and a competent outflow tract.
2. Serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels should be measured to localize the problem to the ovary, pituitary or hypothalamus.
3. **Ovarian Failure**
 - a. Ovarian failure is considered "premature" when it occurs in women less than 40 years of age.
 - b. A LH or FSH level greater than 50 mIU/mL indicates ovarian failure.
4. **Pituitary or Hypothalamic Dysfunction**
 - a. A normal or low gonadotropin level is indicative of pituitary or hypothalamic failure. An MRI is the most sensitive study to rule out a pituitary tumor.
 - b. If MRI does not reveal a tumor, a defect in pulsatile GnRH release from the hypothalamus is the probable cause.

IV. Management of Chronic Anovulation with Adequate Estrogen

- A. Adequate estrogen and anovulation is indicated by withdrawal bleeding with the progesterone challenge test.
- B. Often there is a history of weight loss, psychosocial stress, or excessive exercise. Women usually have a normal or low body weight and normal secondary sex characteristics.
 1. Reducing stress and assuring adequate nutrition may induce ovulation.
 2. These women are at increased risk for endometrial cancer because of the hyperplastic effect of unopposed estrogen.
 3. Progesterone (10 mg per day for the first 7-10 days of every month) is given to induce withdrawal bleeding. If contraception is desired, a low-dose cyclic oral contraceptive may be used.

V. Management of Hypothalamic Dysfunction

- A. Amenorrheic women with a normal prolactin level, a negative progesterone challenge, with low or normal gonadotropin levels, and with a normal sella turcica imaging are considered to have hypothalamic dysfunction. These women have inadequate estrogen and progesterone levels.
- B. Hypothalamic amenorrhea usually results from psychologic stress, depression, severe weight loss, anorexia nervosa, or strenuous exercise.

C. Hormone Therapy for Hypoestrogenic Women

1. Hypoestrogenic women are at a greater risk for osteoporosis and cardiovascular disease.
2. Oral contraceptives are appropriate in young women.
3. Premenopausal women should take conjugated estrogen, 0.625 mg, with medroxyprogesterone (Provera) 2.5 mg, every day of the month.
4. Calcium supplementation is also recommended. Contraception should be used by sexually active women who do not desire pregnancy because pregnancy may still occur in 10%.

VI. Management of Disorders of the Outflow Tract or Uterus

A. Intrauterine Adhesions (Asherman Syndrome) are the most common outflow-tract abnormality that causes amenorrhea.

1. This disorder should be considered if amenorrhea develops following curettage or after endometritis.
2. If adhesions are present on hysterosalpingography, hysteroscopy and lysis of adhesions is performed.

VII. Management of Disorders of the Ovaries

- A.** Ovarian failure should be suspected if menopausal symptoms occur.
- B.** Women with the diagnosis of premature ovarian failure who are less than 30 years of age should undergo karyotyping to rule out the presence of a Y chromosome. If a Y chromosome is detected, testicular tissue, should be sought and removed.
- C.** Women between 30-40 years of age with ovarian failure can usually be assumed to have premature ovarian failure and normal chromosomes.
- D.** Patients with ovarian failure should be prescribed estrogen 0.625 mg with progesterone 2.5 mg daily on every day of the month with calcium.

VIII. Disorders of the Anterior Pituitary

- A.** Prolactin-secreting adenoma are excluded by MRI of the pituitary.
- B.** Bromocriptine (Parlodel) is used for most adenomas; surgery is considered later.

IX. Polycystic Ovarian Syndrome (Hyperandrogenic Chronic Anovulation) is an anovulatory state associated with androgen excess; 70% of patients have polycystic ovaries.

- A.** It is present in 37% of amenorrheic women, and it presents with amenorrhea, hirsutism, and obesity from puberty, but it may also present with irregular and profuse uterine bleeding. These abnormalities are caused by hyperandrogenism and hyperestrogenism.
- B.** Increased levels of testosterone and dehydroepiandrosterone sulfate (DHEA-S) imply PCO; however, circulating androgen levels are sometimes normal in this disorder. Increased LH or an LH/FSH ratio >2.5 can aid in diagnosis.

X. Androgen Secreting Neoplasms

- A.** In women with evidence of hirsutism or virilization, both total testosterone and DHEA-S levels should be determined.
- B.** Total testosterone levels >200 ng/mL or DHEA-S levels >7.0 ng/dL should lead to an investigation for an androgen-secreting neoplasm.

XI. Cushing's Syndrome

- A.** An estimate of cortisol secretion is indicated in women with amenorrhea who present with truncal obesity and striae. Sexual ambiguity may be present.
- B.** Basal level of 17-hydroxyprogesterone or 24-hour urinary excretion of pregnanetriol is warranted if 21-hydroxylase deficiency is suspected.

XII. Androgen Insensitivity Syndrome (Testicular feminization syndrome) is suggested by breast development in the absence of a normal amount of pubic and axillary hair, with a blind ending or absent vagina. These patients usually present during adolescence with primary amenorrhea, and they will not bleed in response to a progesterone/estrogen test. The diagnosis is confirmed by karyotype.

References: See page 148.

Breast Disorders

I. Nipple Discharge

A. Clinical Evaluation

1. Nipple discharge may be a sign of cancer, and it must be evaluated. Eight percent of biopsies performed for nipple discharge demonstrate cancer.
2. Determine the duration, bilaterality or unilaterality of the discharge, and the presence of blood. A history of oral contraceptives, hormone preparations, phenothiazines, nipple or breast stimulation, or lactation should be determined. Discharges that flow spontaneously are more likely to be pathologic than discharges that must be manually expressed.
3. Unilateral, pink colored, bloody or non-milky discharge, or discharges associated with a mass are the discharges of most concern.
4. Bilateral, milky discharge suggest an endocrine problem. Nipple discharge secondary to malignancy is more likely to occur in older patients.
5. **Risk Factors.** A risk assessment should identify risk factors, including age over 50 years, past personal history of breast cancer, history of hyperplasia on previous breast biopsies, and family history of breast cancer in a first-degree relative (mother, sister, daughter).

B. Physical examination should include inspection of the breast for ulceration or contour changes and inspection of the nipple. Palpation should be performed with the patient in both the upright and the supine position to determine the presence of a mass.

C. Diagnostic Evaluation

1. If the discharge appears bloody, the patient should be referred to a surgeon for evaluation. At the time of referral, a mammogram of the involved breast should be obtained if the patient is over 35 years old and has not had a mammogram within the preceding 6 months.
2. Patients with a watery, unilateral discharge should be referred to a surgeon for evaluation and possible biopsy.
3. Non-bloody discharge should be tested for the presence of blood with standard Hemoccult cards. Nipple discharge secondary to carcinoma usually contains hemoglobin.
4. If the discharge appears milky or is bilateral, prolactin and thyroid stimulating hormone assays should be completed to exclude an endocrinologic cause.
 - a. A mammogram should also be performed if the patient is due for routine mammographic screening.
 - b. If results of the mammogram and the endocrinologic screening studies are normal, the patient should return for a follow-up visit in 6 months to ensure that there has been no specific change in the character of the discharge, such as development of bleeding.

II. Breast Pain

- A. Determine the duration and location of the pain, associated trauma, previous breast surgery, associated lumps, or nipple discharge.
- B. Pain is an uncommon presenting symptom for breast cancer; however, cancer must be excluded. Cancer is the etiology in less than 5% of patients with breast pain. Pain that is associated with breast cancer is usually unilateral, intense, and constant.

C. Patients Less Than 35 Years of Age Without a Mass

1. It is unlikely that the pain is a symptom of cancer.
2. A follow-up clinical breast examination is performed in 1-2 months. Diagnostic mammography is usually not helpful but may be considered.

D. Patient 35 Years of Age or Older

1. Obtain diagnostic mammogram, and obtain an ultrasound if the lesion is cystic.
2. If studies are negative, a follow-up examination in 1-2 months is

appropriate.

3. If a suspicious lesion is detected, biopsy is required.

E. Mastodynia

1. Mastodynia is defined as breast pain in the absence of a mass or other pathologic abnormality.
2. **Causes of mastodynia** include menstrually related pain, costochondritis, trauma, and sclerosing adenosis.

III. Fibrocystic Complex

- A. Breast changes are usually multifocal, bilateral, and diffuse. One or more isolated fibrocystic lumps or areas of asymmetry may be present. The areas are usually tender.
- B. This disorder predominantly occurs in women with premenstrual abnormalities, nulliparous women, and nonusers of oral contraceptives.
- C. The disorder usually begins in mid-20's or early 30's. Tenderness is associated with menses and lasts about a week. The upper outer quadrant of the breast is most frequently involved bilaterally.
- D. There is no increased risk of cancer for the majority of patients.
- E. Suspicious areas may be evaluated by fine needle aspiration (FNA) cytology. If mammography and FNA are negative for cancer, and the clinical examination is benign, open biopsy is generally not needed.
- F. **Medical Management of Fibrocystic Complex**
 1. **Oral Contraceptives** are effective for severe breast pain in most young women. Start with a pill that contains low amounts of estrogen and relatively high amounts of progesterone (LoEstrin, LoOvral, Ortho-Cept).
 2. If oral contraceptives do not provide relief, medroxyprogesterone 5-10 mg per day from days 15-25 of each cycle is added.
 3. A professionally fitted support bra often provides significant relief.
 4. **Dietary Changes.** A low fat, caffeine-free diet, vitamins (E and B complex), evening primrose oil, and stopping smoking may provide relief.
 5. NSAIDs and bromocriptine have been used.

References: See page 148.

Menopause

The average age of menopause is 49 years, with a range of 41-55. Menopause before age 41 is considered premature. Menopause is often diagnosed by irregular menses accompanied by hot flashes and an elevated follicle-stimulating hormone (FSH) level.

In the period before menopause, irregular menses begin to occur--shortening, then lengthening, followed by cessation of menses.

I. Climacteric Syndromes

A. Hot Flashes

1. Hot flashes are the most frequently occurring climacteric symptom, and they are characterized by sudden, episodic skin flushing and perspiration.
2. Hot flash frequency varies from less than one daily to 3 episodes per hour, with a duration of 3-4 minutes.

B. Lower Urinary Tract Atrophy

1. After menopause, atrophic changes occur in the urethra and periurethra. Loss of pelvic tone and prolapse of the urethrovesicular junction occurs.
2. Dysuria, urgency, frequency, suprapubic discomfort, stress, and urge incontinence are frequent.

C. Genital Changes

1. Shortening of the vaginal canal, loss of rugae, epithelial thinning and

friability, and bacterial vaginoses are common.

2. Atrophic vaginitis, dyspareunia, or vaginal bleeding may occur.

D. Osteoporosis. Menopause is associated with decreased bone mass and increased susceptibility to fractures; estrogen supplementation decreases fracture risk by 50%.

E. Cardiovascular System. Estrogen replacement offers protection from cardiovascular disease in menopausal women.

II. Laboratory Tests

A. Menopause may be confirmed by a FSH serum level greater than 30 mIU/mL. Estradiol should be measured to assure proper timing; the level should be <75 pcg/mL.

B. Laboratory tests are sometimes indicated to exclude other diagnoses that may cause amenorrhea (thyroid disease, hyperprolactinemia, pregnancy).

C. A lipid profile, Pap smear, mammogram, and stool guaiac are indicated for routine screening.

D. Bone density measurements are not usually needed. For woman who are undecided about hormone replacement therapy, dual-energy x-ray absorptiometry can help the patient to make a more informed decision.

III. Overview of Menopause Treatment

A. Women who are still menstruating are eligible for hormone replacement therapy (HRT) if perimenopausal and troubled by symptoms of menopause.

B. Estrogen replacement should be continued indefinitely, because stopping therapy results in rapid loss of bone. There is no upper age limit for starting estrogen replacement.

C. Breast Cancer Risk. Breast cancer risk is not significantly increased by hormone therapy in women who do not have a family history of breast cancer. However, estrogen therapy is not recommended for women with a family history of breast cancer in a first-degree relative.

D. Contraindications to Estrogen Replacement Therapy

1. Previously diagnosed or suspected breast cancer
2. Previously diagnosed or suspected endometrial cancer
3. Active liver disease
4. Active thromboembolic disease

IV. Hormone Replacement Therapy Regimens

A. Estrogen and Progestin Therapy for Patients with Uterus Present

1. Estrogen should be administered daily (continuous regimen). An interruption of therapy at the end of each month (cyclic regimen) is not necessary.

2. Progestins are added to prevent endometrial hyperplasia and to minimize the risk of uterine cancer. Progesterone is not indicated for women without a uterus.

3. Continuous Therapy

a. **Conjugated estrogens (Premarin)** 0.625 mg PO daily and medroxyprogesterone acetate (Provera), 2.5 mg daily continuously.

b. **Combination Estrogen with Progestin (Prempro)**, 0.625 mg of estrogen and 2.5 mg of medroxyprogesterone in one tablet daily, continuously.

c. Some spotting and bleeding is expected initially, but amenorrhea occurs in 40% of women within 3 months.

d. In women who continue to experience spotting or bleeding 3 months after the start of continuous estrogen replacement therapy, the dosage of medroxyprogesterone may be increased to 5 mg daily. If bleeding continues after 6 months at this dosage, the dosage may be increased to 10 mg per day.

e. Follow-up endometrial biopsies are not routinely necessary. If irregular bleeding occurs after the establishment of amenorrhea, endometrial biopsy is necessary.

4. Cyclical Therapy

a. An easy cyclic schedule consists of estrogen (Premarin), 0.625 mg

every day of month, with medroxyprogesterone (Provera), 5-10 mg added for first 2 weeks of each month. Some women prefer to take progesterone only every 2-3 months to reduce the frequency of menses.

- b. Another cyclic regimen consists of estrogen (Premarin), 0.625 mg, on days 1 through 25, and medroxyprogesterone (Provera), 5-10 mg on days 12 through 25.

B. Hormone Replacement Side Effects

1. Gastrointestinal symptoms due to estrogen (nausea) may respond to a switch to transdermal estrogen, 0.5 mg patch, twice weekly.
2. Progestogens are associated with bloating, cramping, and irritability. Decreasing the daily progestogen dosage, or taking it on alternate days may help alleviate these symptoms.

V. Additional Menopausal Therapy

A. Calcium and Vitamin D

1. Calcium intake should be at least 1,500 mg/day, including dietary intake. Calcium supplementation is necessary for most women, especially those with poor dietary intake.
2. Vitamin D at 400 IU per day is recommended for patients with limited exposure to sunshine who do not drink Vitamin D fortified milk (especially elderly nursing home residents).

- B. Exercise.** Healthy woman should exercise at least 3 times a week for 30 minutes.

C. Atrophic Vaginitis

1. Local application of estrogen (0.6 mg of conjugated estrogen cream--about 1/4 of an applicator) daily for 1-2 weeks, then 2-3 times/week will usually relieve urogenital symptoms.
2. This regimen is used concomitantly with oral estrogen.

References: See page 148.

Osteoporosis

Osteoporosis is characterized by reduced bone mass leading to an increased risk of fracture. The best way to manage osteoporosis is through prevention.

I. Pathophysiology

- A.** After menopause, women experience bone loss of 3-4% per year. If bone loss is not stopped, 90% of women will have osteoporosis by age 80.
- B.** After age 50, the risk of hip fracture doubles every 5 to 10 years.
- C.** The incidence of osteoporosis is higher in women than in men because of lower peak bone mass and a more rapid loss of bone.

II. Risk Factors for Osteoporosis

- A.** White and Asian women have a higher risk than black women. Slender build and low body weight also increase risk.
- B.** Prolonged estrogen deficiency and amenorrhea can lead to bone loss in young women.
- C.** A diet low in calcium, sedentary lifestyle, cigarette smoking, and excessive alcohol use increase the risk of osteoporosis.
- D.** Women who have suffered a fracture of any type have twice the average risk of having another fracture.
- E. Medications That Predispose to Osteoporosis.** Phenytoin (Dilantin), excessive thyroid hormone, systemic corticosteroids, long-term use of inhaled corticosteroids, prolonged use of depo-medroxyprogesterone (Depo-Provera)

III. Diagnosis of Osteoporosis

- A.** Osteoporosis may be apparent when radiographs are taken for an unrelated reason.
- B. History** should include age at onset of menopause (natural or surgical),

calcium intake, level of physical activity, family history of osteoporosis, presence of other medical conditions, medications, and back pain.

- C. **Physical Examination.** Spinal deformity, tenderness, and immobility are assessed.
- D. **Laboratory Testing** to exclude secondary causes of osteoporosis may include a biochemical profile, complete blood count, thyroid function tests, serum and urine protein immunoelectrophoresis, testosterone level (in men), and 24-hour urinary calcium, cortisol, and creatinine excretion.
- E. **Bone Mineral Density Testing**
 - 1. Dual-energy x-ray absorptiometry (DEXA) is the best choice for measurement of bone mineral density because it is the most precise and requires the lowest dose of radiation.
 - 2. Bone mineral density testing is indicated for patients who refuse hormone replacement therapy, because results can substantially influence a woman's decision.
 - 3. Periodic testing is not routinely indicated during treatment unless it improves adherence.

IV. Treatment of Established Osteoporosis

- A. Calcium carbonate (Tums), one 500 mg tab, 2 times a day, and vitamin D 400 units daily should be prescribed. Intake of 1500 mg/day of calcium is recommended.
- B. **Hormone Replacement Therapy**
 - 1. Estrogen is the treatment of choice for both prevention and treatment of osteoporosis. Therapy can result in a 5-15% increase in bone mineral density after 3 years.
 - 2. No significant increased risk of breast cancer has been found; however, women with a family history of breast cancer in a first-degree relative should probably not be given estrogen.
 - 3. Estrogen has a cardiovascular protective effect, which may decrease the occurrence of ischemic heart disease by 50%.
 - 4. **Estrogen Regimens**
 - a. Conjugated estrogen (Premarin) 0.625 mg daily and medroxyprogesterone (Provera) 2.5 mg daily.
 - b. Combination estrogen and progesterone (Prempro), 0.625 mg of estrogen and 2.5 mg of medroxyprogesterone in one tablet, taken daily.
 - 5. **Estrogen Contraindications.** History of uterine or breast cancer, history of thromboembolism, abnormal liver function.
- C. **Bisphosphonates--Alendronate (Fosamax)**
 - 1. Alendronate reduces the risk of hip and spine fractures by decreasing the rate of bone resorption, increasing bone density 3% per year.
 - 2. Alendronate is indicated for women with osteoporosis who can not take estrogen. Since it is not a hormone, alendronate may be suitable for men and for women with a personal or family history of breast cancer. Alendronate does not have the cardiovascular protective effects of estrogen.
 - 3. **Dosage.** 10 mg a day before breakfast. Alendronate is poorly absorbed; therefore, it must be taken 1 hour before drinking coffee or juice, and before eating any food, or taking any other medication. The patient must remain upright for 30 minutes to prevent esophagitis.
 - 4. The incidence of side effects is acceptable, with GI upset being the most common.
- D. **Calcitonin**
 - 1. Calcitonin (Miacalcin) is an alternative for women who are unable to use estrogen or alendronate. Calcitonin has weaker effects on bone than estrogen.
 - 2. Calcitonin has an analgesic effect, which may make it useful for women with chronic back pain. Calcitonin does not offer the additional protective effects of estrogen, such as cessation of menopausal

118 Abnormal Uterine Bleeding

symptoms or cardiovascular protection.

3. Dosage is 200 IU (one spray) per day in alternating nostrils.

V. Prevention of Osteoporosis

A. Calcium Intake

1. 1,500 mg per day of calcium is recommended for postmenopausal women.
2. If a patient's diet does not provide adequate calcium, supplementation should be recommended. Calcium carbonate (Tums) provides the most elemental calcium per gram. It is best absorbed if taken with meals as one 500 mg tab, 2 times a day.
3. Calcium supplementation is contraindicated in patients with a history of nephrolithiasis, sarcoidosis, hyperparathyroidism, and certain malignancies causing hypercalcemia.

B. Vitamin D

1. Vitamin D is required for calcium absorption and is synthesized after exposure to sunlight.
2. The recommended daily allowance is 400 U; most multivitamins contain this amount. Milk contains 100 U of vitamin D per cup.
3. Vitamin D is recommended for housebound elderly patients and those living in nursing homes. Persons who live in the northern states may also benefit from supplements during the winter months.

C. Exercise: Weight-bearing exercise helps maintain bone mass and should be recommended to all patients able to comply.

D. Estrogen therapy stops or slows bone loss, even after age 80. Use reduces vertebral fractures by about 50-80%.

References: See page 148.

Abnormal Uterine Bleeding

Although menorrhagia is occasionally caused by potentially treatable diseases, such as thyroid dysfunction, infections or cancer, the excessive bleeding is most often related to anovulatory menstrual cycles. Menorrhagia caused by anovulation is referred to as dysfunctional uterine bleeding.

I. Pathophysiology of Normal Menstruation

- A. In response to gonadotropin-releasing hormone from the hypothalamus, the pituitary gland synthesizes follicle-stimulating hormone (FSH) and luteinizing hormone (LH) which induce the ovaries to produce estrogen and progesterone.
- B. During the follicular phase, estrogen stimulation causes an increase in endometrial thickness. After ovulation, progesterone causes endometrial maturation and secretory changes.
- C. **Abnormal Bleeding** is characterized by bleeding that occurs at intervals of less than 21 days, more than 36 days, lasting longer than 7 days, or blood loss greater than 80 mL.

II. Clinical Evaluation of Abnormal Uterine Bleeding

- A. Obtain a menstrual and reproductive history, including last menstrual period, regularity, duration, and frequency; ascertain the number of pads used per day, and ask about intermenstrual bleeding.
- B. Assess the presence of stress, exercise, weight changes, and systemic diseases, particularly thyroid, renal or hepatic diseases, or coagulopathies.
- C. The method of birth control should be determined.
- D. Pregnancy complications, such as spontaneous abortion, ectopic pregnancy, placenta previa and abruptio placentae, can all cause non-cyclical, heavy bleeding. Pregnancy should always be considered as a possible cause of abnormal uterine bleeding.

E. Determine whether the patient is having ovulatory or anovulatory cycles

1. Ovulatory cycles are characterized by menstrual flows occurring at regular intervals, preceded by premenstrual symptoms (breast tenderness or fullness, pelvic cramping, and edema).
2. If cycles are anovulatory, the patient has dysfunctional uterine bleeding.

F. The clinical approach to abnormal uterine bleeding involves dividing patients into three age groups:

1. **Puberty and Adolescence.** Menarche to age 16
2. **Primary Childbearing Years.** Ages 16 to early 40's
3. **Premenopausal, Perimenopausal, and Postmenopausal Years.** Early 40's and older

III. Puberty and Adolescence

- A. Irregularity is normal during the first few months of menstruation; however, soaking more than 25 pads or 30 tampons during a menstrual period is abnormal.
- B. Absence of premenstrual symptoms (breast tenderness, bloating, cramping) is associated with anovulatory cycles.
- C. Fever, particularly in association with pelvic or abdominal pain or dyspareunia, may indicate pelvic inflammatory disease.
- D. A history of easy bruising suggest a coagulation defect. Headaches and visual changes suggest a CNS cause, such as a pituitary tumor.

E. Physical Findings

1. Pallor not associated with tachycardia or signs of hypovolemia suggests chronic excessive blood loss, such as that occurring with anovulatory bleeding, adenomyosis, uterine myomas, or blood dyscrasia.
2. Signs of impending shock indicate that the blood loss is likely related to pregnancy (including ectopic), trauma, sepsis, or neoplasia.
3. Pelvic masses may represent pregnancy, uterine or ovarian neoplasia, or a pelvic abscess or hematoma.
4. Fever, leukocytosis, and pelvic tenderness suggests PID.
5. Fine, thinning hair, and hypoactive reflexes suggest hypothyroidism.
6. Ecchymoses or multiple bruises may indicate trauma, coagulation defects, medication use, or dietary extremes.

F. Laboratory Tests

1. CBC and platelet count, urinalysis, Pap smear, and a urine or serum pregnancy test are completed.
2. Screening for sexually transmitted diseases, thyroid function, and coagulation disorders (partial thromboplastin time, prothrombin time, and bleeding time) is necessary.
3. **Endometrial sampling** is rarely necessary for those under age 20.

G. Treatment of Infrequent Bleeding

1. Therapy should be directed at the underlying cause when possible.
2. If the CBC and results of other initial laboratory tests are normal, and the history and physical examination are normal, reassurance is usually all that is necessary.
3. Ferrous sulfate, 325 mg bid-tid.

H. Treatment for Frequent or Heavy Bleeding

1. Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandins in the endometrium, improve platelet aggregation, and increase uterine vasoconstriction.
2. NSAIDs are the first choice in the treatment of menorrhagia, because they are well tolerated, associated with a low incidence of side effects, and they do not have the hormonal effects of oral contraceptives. Additionally, women with menorrhagia frequently also have dysmenorrhea, and NSAIDs are effective for this problem.
3. **Specific Agents**
 - a. Mefenamic acid (Ponstel), 500 mg tid daily for 3 days during the menstrual period.

120 Abnormal Uterine Bleeding

- b. Naproxen (Anaprox, Naprosyn), a 500-mg loading dose, then 250 mg three times daily for 5 days.
- c. Ibuprofen (Motrin, Nuprin), 400-600 mg tid during the menstrual period.
- d. These agents are equally effective.
- e. Gastrointestinal distress is common, and these agents are contraindicated in renal failure and peptic ulcer disease.

4. Iron therapy should be added; 325 mg qd-tid.

I. Patients with hypovolemia or a hemoglobin level below 7 g/dL should be hospitalized for hormonal therapy, iron replacement, and possibly transfusion.

1. Hormonal therapy consists of estrogen (Premarin) 25 mg IV q6h until bleeding stops. Begin oral contraceptive pills q6h x 7 days, then taper slowly.
2. If bleeding continues, IV vasopressin (DDAVP) is used. Hysteroscopy may be necessary. Dilation and curettage is a last resort.

IV. Primary Childbearing Years

A. Contraceptive complications and pregnancy are the most common causes of abnormal bleeding in this age group. Anovulatory conditions account for 20% of cases.

B. Adenomyosis, endometriosis, and fibroids increase in frequency as a woman ages, as do endometrial hyperplasia and endometrial polyps. PID, endocrine dysfunction, and all other causes may sometimes occur.

C. Laboratory Tests

1. CBC and platelet count, urinalysis, Pap smear, and a pregnancy test.
2. Screening for sexually transmitted diseases, thyroid dysfunction, and coagulation disorders (partial thromboplastin time, INR, bleeding time) is completed.
3. If a non-pregnant woman has a pelvic mass, evaluation is required with ultrasonography or hysterosonography (with uterine saline infusion), and, if necessary, CT, or laparoscopy.

D. Endometrial Sampling

1. Long-term unopposed estrogen stimulation in anovulatory patients can result in endometrial hyperplasia, which can progress to adenocarcinoma; therefore, in perimenopausal patients who have been anovulatory for an extended interval, the endometrium should be biopsied.
2. Biopsy is also carried out before initiation of hormonal therapy for women over age 30 and for those over age 20 who have prolonged bleeding. Risk factors for endometrial hyperplasia include anovulation, obesity, and infertility or decreased parity.
3. Endometrial biopsy with Pipelle should be done on the first day of menstruation, to avoid an unexpected pregnancy, or anytime if bleeding is continuous. If hysteroscopy is done first, it will reveal up to 30% of abnormalities that would be missed by endometrial sampling. Hysterosonography with uterine saline infusion may also be used.

E. Patients with pelvic masses usually require an ultrasound.

F. Treatment

1. Medical protocols for anovulatory bleeding (dysfunctional uterine bleeding) are similar to those above.
2. **Hormonal Therapy**
 - a. In women who do not desire immediate fertility, hormonal therapy may be used to treat menorrhagia.
 - b. A 21-day package of oral contraceptives, containing 35 mcg of estrogen (Ortho-Novum 1/30), is used. Have the patient take one pill three times a day for 7 days. During the 7 days of therapy, bleeding should subside and, following treatment, heavy flow will occur. After 7 days off the hormones, another 21-day package is initiated, taking one pill a day for 21 days, then no pills for 7 days.

- c. Alternatively, a cyclic regimen of medroxyprogesterone (Provera), 10-20 mg per day for days 16 through 25 of each month also results in a reduction of menstrual blood loss. Pregnancy will not be prevented.
- 3. Iron therapy should be added; 325 mg qd-tid.
- 4. Surgical treatment can be considered if childbearing is completed and medical management fails to provide relief.

V. Patients Age 40 and Over

- A. Anovulatory bleeding accounts for about 90% of abnormal uterine bleeding in this age group. However, bleeding should be considered to be from cancer until proven otherwise.
- B. History, physical examination, and laboratory testing are indicated as described above.
- C. Menopausal symptoms, personal or family history of malignancy, and use of estrogen should be sought.
- D. If a woman has a pelvic mass, an evaluation with ultrasonography, CT, and/or MRI is necessary.

E. Endometrial Carcinoma

- 1. In a perimenopausal or postmenopausal woman, amenorrhea preceding abnormal bleeding suggests a malignancy of the endometrium.
- 2. Endometrial evaluation is necessary before treatment for abnormal uterine bleeding.
- 3. Before endometrial sampling, determination of endometrial thickness by transvaginal ultrasonography is useful because biopsy is often not required when the endometrium is less than 5 mm thick. An endometrium thicker than 5-6 mm in a postmenopausal patient requires biopsy.

F. Treatment

- 1. Cystic hyperplasia or endometrial hyperplasia without cytologic atypia is treated with depo-medroxyprogesterone. Start with 200 mg IM, then give 100 to 200 mg IM every 3 to 4 weeks for 6 to 12 months. Endometrial hyperplasia requires repeat endometrial biopsy every 3 to 6 months.
- 2. Atypical hyperplasia requires fractional dilation and curettage, followed by progestin therapy or hysterectomy.
- 3. If the patient's endometrium is normal (or atrophic) and contraception is a concern, lower-dose oral contraceptive products may be used. If contraception is not needed, estrogen replacement therapy should be prescribed.
- 4. **Surgical Management**
 - a. **Vaginal or Abdominal Hysterectomy** is the most absolute curative treatment.
 - b. **Dilatation and Curettage** is used only as a temporizing measure.
 - c. **Endometrial Ablation and Resection** by laser, electrodiathermy "rollerball," or excisional resection are alternatives to hysterectomy.

References: See page 148.

Pelvic Inflammatory Disease

One in 10 women has pelvic inflammatory disease (PID) during her reproductive years. At least one-fourth of women with PID have serious sequelae, such as infertility, ectopic pregnancy or chronic pelvic pain.

PID includes endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis.

I. Microbiology

- A. PID is usually polymicrobial, including both aerobic and nonaerobic bac-

teria.

- B. Sexually transmissible organisms most frequently implicated include *Neisseria gonorrhoeae* and *Chlamydia trachomatis*.
- C. *Mycoplasma hominis* and *Ureaplasma urealyticum* have occasionally been isolated. *Escherichia coli*, streptococcal species, and anaerobes, all part of the normal flora, have been implicated.

II. Diagnosis

- A. The diagnosis of PID relies on a high index of suspicion. PID is correctly diagnosed on the basis of clinical and laboratory indicators in only 65% of cases. Therefore, a low threshold for initiating empiric antibiotics is essential.
- B. Risk factors include multiple sex partners, frequent sexual intercourse, and the acquisition of a new sexual partner within the previous 3 months.
- C. PID is characterized by diffuse lower abdominal pain that is often dull and constant, usually bilateral, and less than 2 weeks in duration.
- D. An abnormal vaginal discharge, abnormal bleeding, dysuria, dyspareunia, nausea, vomiting, or fever may be present. PID is more likely to begin during the first half of the menstrual cycle.
- E. Abdominal tenderness, adnexal tenderness, and cervical motion tenderness are the most frequently observed findings.
- F. The presence of symptoms, lower abdominal tenderness, adnexal tenderness, and cervical motion tenderness is sufficient evidence to justify beginning empiric therapy for suspected PID.

Differential Diagnosis of PID

Appendicitis Ectopic pregnancy Hemorrhagic ovarian cyst Ovarian torsion Endometriosis Urinary tract Infection	Irritable bowel syndrome Somatization Gastroenteritis Cholecystitis Nephrolithiasis
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III. Laboratory Evaluation

- A. Laboratory studies may be entirely normal. An elevated leukocyte count does not distinguish PID from other diagnoses.
- B. Cervical cultures for gonorrhea or Chlamydia require 3-7 days for results.
- C. Despite the good specificity of nonculture tests (eg, Chlamydiazyme, Sure Cell Chlamydia), sensitivity remains less than optimal.
- D. Human immunodeficiency virus (HIV) and syphilis testing should be recommended for patients with suspected PID.
- E. Pelvic ultrasonography can detect pelvic abscesses.
- F. Laparoscopy is the "gold standard" for diagnosing PID, and it is recommended when the diagnosis is unclear or when the patient fails to improve.

IV. Treatment and Supportive Care

- A. **Antibiotic Therapy** should be initiated as soon as the diagnosis of PID is suspected, usually before culture results are available.
- B. **CDC Guidelines for Outpatient Treatment of PID**
 - 1. **Ceftriaxone-Doxycycline Regimen**
 - a. Ceftriaxone (Rocephin), 250 mg IM (or other parenteral third-generation cephalosporin), or Cefoxitin (Mefoxin), 2 gm IM plus probenecid (Benemid), 1 gm PO in a single dose
Plus
 - b. Doxycycline (Vibramycin), 100 mg PO bid for 14 days.
 - 2. **Ofloxacin-Clindamycin Regimen**
 - a. Ofloxacin (Floxin), 400 mg PO bid for 14 days
Plus
 - b. Clindamycin (Cleocin), 450 mg PO qid, or metronidazole (Flagyl),

500 mg PO bid, for 14 days.

C. CDC Guidelines for Inpatient Treatment of PID

1. Cefoxitin-Doxycycline Regimen

a. Cefoxitin (Mefoxin), 2 g IV q6h, or cefotetan (Cefotan), 2 g IV q12h
Plus

b. Doxycycline (Vibramycin), 100 mg IV q12h.

2. Clindamycin-Gentamicin Regimen

a. Clindamycin (Cleocin), 900 mg IV q8h
Plus

b. Gentamicin (Garamycin), loading dose 2 mg/kg IV/IM, followed by 1.5 mg/kg IV/IM q8h.

3. Intravenous therapy should be continued for at least 48 hours after clinical improvement. Thereafter, **doxycycline**, 100 mg PO bid, is given for a total of 14 days. If tubo-ovarian abscess is present, clindamycin is used for continued therapy, rather than doxycycline.

4. The cefoxitin-doxycycline regimen is superior if Chlamydia is suspected as the primary pathogen.

5. The clindamycin-gentamicin regimen has the advantage when more effective anaerobic coverage is desired, such as in patients with suspected tubo-ovarian or pelvic abscesses.

6. Adequate hydration and analgesia should also be provided.

D. Partner Referral. Sexual contacts should be treated for GC and Chlamydia, without regard to clinical or laboratory results.

References: See page 148.

Sexually Transmitted Diseases

I. Gonorrhea

A. Gonorrhea causes urethral, cervical, rectal, or pharyngeal infections.

B. Indications for Immediate Empiric Treatment

1. Mucopurulent cervicitis
2. Pelvic inflammatory disease
3. Contacts to GC or to presumptive GC infection
4. Treatment of partners should be provided

C. Diagnostic Labs

1. Culture is recommended for public health purposes.
2. Test of cure is not necessary.
3. Serologic testing for syphilis and HIV should be considered.

D. Recommended Treatment of Uncomplicated Infections

1. Ceftriaxone (Rocephin) 250 mg IM; active against incubating syphilis **OR**
2. Cefixime (Suprax) 400 mg po; active against incubating syphilis **OR**
3. Ciprofloxacin (Cipro) 500 mg po; contraindicated <17 years of age; not active against syphilis **OR**
4. Ofloxacin (Floxin) 400 mg po; contraindicated <17 years of age; not active against syphilis.

Plus

5. Doxycycline 100 mg po bid x 7 days; for coexisting Chlamydia trachomatis infection; may abort incubating syphilis.

E. Alternative Regimens

1. Ceftizoxime 500 mg IM, cefotaxime 500 mg IM, cefotetan 1 g IM, cefoxitin 2 g IM, cefuroxime axetil (Ceftin) 1 g po, cefpodoxime 200 mg po.
2. Enoxacin 400 mg po, lomefloxacin 400 mg po, or norfloxacin 800 mg po
plus
3. Doxycycline 100 mg po bid x 7d.

II. Chlamydia Trachomatis

- A. Chlamydia may cause urethritis, cervicitis, conjunctivitis, or proctitis.
- B. **Diagnostic Labs**
 - 1. Culture and nonculture techniques for chlamydia are available.
 - 2. Test of cure is not necessary if a recommended regimen was used.
 - 3. Serologic testing for syphilis and HIV should be considered.
- C. **Recommended Treatment**
 - 1. Azithromycin (Zithromax) 1 g po x 1 dose **OR**
 - 2. Doxycycline 100 mg po bid x 7 days
- D. **Alternative Regimens**
 - 1. Ofloxacin (Floxin) 300 mg po bid x 7 days
 - 2. **Pregnancy**
 - a. Erythromycin base 500 mg PO qid x 7 days **OR**
 - b. Amoxicillin 500 mg PO tid x 10 days **OR**
 - c. Azithromycin (Zithromax) 1 g po x 1 dose.
 - 3. Test of cure should be completed if alternative regimens are used.

References: See page 148.

Vaginal Infections

I. Clinical Evaluation of Vaginal Symptoms

- A. The type and extent of symptoms, such as itching, discharge, odor, or pelvic pain should be determined.
- B. A change in sexual partners or sexual activity, changes in contraception method, medications (antibiotics), and history of prior genital infections, in the patient or partner, should be noted. The possibility of pregnancy should be assessed.
- C. **Physical Examination**
 - 1. Examine for lesions on the perineum, vulva, vagina or cervix.
 - 2. The color, texture, and odor of vaginal or cervical discharge is noted.
 - 3. **Saline Wet Mount**
 - a. Use one swab to obtain a sample from the posterior vaginal fornix, obtaining a "clump" of discharge. Place the sample on a slide, add one drop of normal saline, and apply a coverslip.
 - b. Coccoid bacteria and clue cells (bacteria-coated, stippled, epithelial cells) are characteristic of bacterial vaginosis.
 - c. Trichomoniasis is confirmed by identification of trichomonads--motile, oval flagellates. White blood cells are prevalent.
 - 4. **Potassium Hydroxide (KOH) Preparation**
 - a. Place a second sample on another slide. One drop of 10% potassium hydroxide (KOH) and a coverslip are applied. A pungent, fishy odor upon addition of KOH--a positive whiff test--strongly indicates bacterial vaginosis.
 - b. The KOH prep may reveal Candida in the form of thread-like hyphae and budding yeast.
 - 5. **Cultures** are not routinely indicated.
- D. **Screening for STDs.** Testing and treatment for gonorrhea and chlamydial infection should be considered for women with either a new sexual partner, purulent cervical discharge, or cervical motion tenderness.

II. Differential Diagnosis

- A. The most common cause of vaginitis is bacterial vaginosis, followed by Candida albicans, with trichomoniasis on the decline.
- B. Common nonvaginal etiologies include contact dermatitis from spermicidal creams, latex in condoms, or douching. Any STD can produce vaginal discharge.

III. Bacterial Vaginosis

- A. Bacterial vaginosis develops when a shift in the normal vaginal ecosystem

results in replacement of the usually predominant lactobacilli with mixed bacterial flora. Bacterial vaginosis is the most common type of vaginitis.

- B. Transmission is both sexual and non-sexual.
- C. There is usually little or no inflammation of the vulva or vaginal epithelium. There is little itching, no pain, and the symptoms tend to have an indolent course with chronic vaginal discharge and a "fishy" postcoital odor.
- D. **Diagnostic Findings**
 - 1. Clue cells (saline slide shows epithelial cells stippled with bacteria).
 - 2. Positive whiff test (fishy odor with KOH).
 - 3. Homogeneous, white, adherent discharge.
 - 4. Culture has a poor specificity.
- E. **Treatment Regimens**
 - 1. **Metronidazole (Flagyl)** 500 mg bid x 7 days. A single oral dose of 2 g has a lower cure rate than the 7 day regimen.
 - a. **Side Effects.** Nausea, heartburn, metallic taste. Emetic effect with alcohol (Antabuse effect).
 - b. Contraindicated in the first trimester of pregnancy because of a small teratogenic potential.
 - 2. **Topical Therapies**
 - a. Topical therapies have a 90% cure rate. Mineral oil base may weaken latex condoms and contraceptive diaphragms.
 - b. Metronidazole gel (MetroGel), one applicatorful (5 g) bid, morning and evening, for 5 days.
 - c. Clindamycin cream, 2% (Cleocin), one applicatorful (2 g) at bedtime for 7 nights.
 - 3. Routine treatment of sexual partners is not necessary, but is sometimes helpful for patients with frequent recurrences.
 - 4. Evaluate for other STD's.
 - 5. Multiple recurrences are not uncommon (30% within 3 mos).
- F. **Persistent Cases.** Reevaluate and exclude other infections, including trichomonas.
 - 1. Clindamycin, 300 mg orally bid for 7 days.
 - 2. Treat sexual partners.

IV. **Candida Vulvovaginitis**

- A. Candida is the second most common diagnosis associated with vaginal symptoms. It is found in 25% of asymptomatic women. Fungal infections account for less than 33% of all vaginal infections.
- B. **Possible Risk Factors.** Use of oral contraceptives, antibiotics, diabetes, intestinal colonization by candida, tight clothing, and immunologic defects.
- C. **Symptoms and Signs.** Marked itching, thick, white, odorless discharge; vulvar or vaginal erythema. Thrush appears as white plaques loosely attached to mucous membranes.
- D. **Potassium Hydroxide Preparation** reveals hyphae or budding yeast. Rapid tests for Candida antigens are more sensitive than KOH preparation.
- E. Candida on Pap smear is specific but not sensitive.
- F. **Treatment of Candida Vulvovaginitis**
 - 1. For severe symptoms and chronic infections, a 7-day course of treatment is used, instead of a 1 day or 3 day course. If there is extensive vulvar involvement, a cream is used instead of a suppository.
 - a. Terconazole (Terazol 7), 0.4% cream, one applicatorful intravaginally for 7 nights; or (Terazol 3) 0.8% cream, one applicatorful intravaginally for 3 nights; or 80 mg suppository, 1 suppository for 3 nights; terconazole is a triazole, which is superior to treatment with other topical agents.
 - b. Butoconazole (Femstat) 2% cream, one applicatorful intravaginally for 3-6 nights.
 - c. Miconazole (Monistat 7) 2% cream, one applicatorful intravaginally for 7 nights (OTC); or 200 mg vaginal suppository, one suppository for 3 nights; or 100 mg vaginal suppository, one suppository for 7

126 Vaginal Infections

nights (OTC).

- d. Clotrimazole (Gyne-Lotrimin) 1% cream, one applicatorful intravaginally for 7 nights; or 100 mg vaginal tablet for 7 nights (OTC); or 100 mg vaginal tablet, two tablets for 3 nights; or 500 mg vaginal tablet, one tablet single application.
- e. Creams and suppositories are oil-based and may weaken latex condoms and diaphragms.

2. Pregnancy: Miconazole or clotrimazole are used.

G. Oral Regimens for Resistant or Recurrent Candida

1. Fluconazole (Diflucan), 150 mg PO one time [150 mg].
2. Ketoconazole (Nizoral), 200 mg PO bid for 5 days.
3. Itraconazole (Sporanox), 100 mg PO qd for 3 days.

H. Resistant or Recurrent Cases

1. Reexamine and repeat topical therapy for a 14-21-day course. Oral regimens have the potential for eradicating rectal reservoirs.
2. Patients with recalcitrant disease should be evaluated for diabetes and HIV.

I. Prophylactic Regimens for Frequent Infections

1. Fluconazole (Diflucan), 100-150 mg PO once a week [100,150 mg].
2. Clotrimazole (Gyne-Lotrimin), one 500-mg vaginal tablet once a week.
3. Ketoconazole (Nizoral), 100 mg PO once a week.

J. Personal Practices. Loose-fitting, cotton undergarments and use of sanitary napkins rather than tampons are recommended. Patients should be advise against douching.

V. Trichomonas Vaginitis

- A. Trichomonas, a flagellated anaerobic protozoan, is a sexually transmitted disease with a high transmission rate. Non-sexual transmission is possible because the organism can survive a few hours in a moist environment.
- B. This disease elicits severe vaginal and vulvar itching and irritation, dysuria, dyspareunia, and an abnormal vaginal odor.
- C. Fiery red vaginal mucosa and a profuse, yellow-green, bubbly, vaginal discharge is common. A strawberry cervix (scattered red macules) is uncommonly seen. The disease is asymptomatic in 50% of women and 90% of men.
- D. **Diagnosis.** Motile trichomonads are observed on normal saline preparation; >10 white blood cells per high-power field is common. Diagnosis of trichomonas by Pap smear is unreliable and should be confirmed with a saline preparation. Culture documentation is usually not required.

E. Treatment of Trichomonas Vaginitis

1. Metronidazole (Flagyl), 2 g PO in a single dose for both the patient and sexual partner, or 500 mg PO bid for 7 days, or 250 mg tid for 7 days; should be taken with food to avoid GI upset.
2. Topical therapy is not recommended because the organism may persist in the urethra and Skene's glands after local therapy.
3. Evaluate for coexisting sexually transmitted diseases.
4. **Persistent Cases.** Consider noncompliance, reinfection, metronidazole resistance, inaccurate diagnosis, or infection with multiple sexually transmitted diseases.
5. If persistence of trichomonas occurs, the patient and partner are retreated using standard dosages. Higher dosages of metronidazole, 2 g PO qd for three days or 500 g PO bid for 14 days with intravaginal metronidazole gel (MetroGel), 5 g intravaginally bid for 5 days, may be necessary.
6. **Pregnancy.** Clotrimazole 100 mg vaginally qhs x 7-14 d.

VI. Other Diagnoses Causing Vaginal Symptoms

- A. One-third of patients with vaginal symptoms will not have laboratory evidence of bacterial vaginosis, Candida, or trichomonas.
- B. Other causes of the vaginal symptoms should be considered, including

cervicitis, allergic reactions, and vulvodynia.

- C. **Atrophic Vaginitis** should be considered in postmenopausal patients. The mucosa appears pale and thin; wet-mount findings will be negative. Topical estrogen cream is applied; it is usually taken concomitantly with oral hormone replacement.
- D. **Allergy** is an unusual cause of vaginal symptoms, sometimes resulting from *Candida* or semen allergy. Systemic antihistamines may be helpful.

References: See page 148.

Pubic Infections

I. Human Papilloma Virus

- A. HPV is the most common tumor of the vulva. The incubation period varies from weeks to months.

B. Clinical Evaluation

- 1. Condyloma acuminata lesions are characterized by rough, verrucous papillomas on the genitalia.
- 2. Enlargement often occurs during pregnancy and sometimes lesions disappear spontaneously.
- 3. No practical screening tests for subclinical infection exist. Pap smear diagnosis of HPV does not correlate well with detection of HPV DNA.

C. Treatment of Genital/Perianal Warts

- 1. **Cryosurgery with liquid nitrogen or cryoprobe** is more effective than topical therapies. Lesions should be frozen until a 2 mm margin of freeze appears, then allowed to thaw, then refrozen. Repeat freeze several times.
- 2. **Podophyllin** 25% in of benzoin may be applied and washed off 4 hours later. Two or 3 applications, 1 week apart, may be needed. Podophyllin should not be used on the vagina or cervix; contraindicated in pregnancy.
- 3. **Trichloroacetic acid (80%)**. Apply to lesion with a cotton-tip applicator, then observe for 5-10 minutes; 2 or 3 applications may be needed, 1 week apart. Burning is common. TCA can be used on the cervix, vaginal sidewalls, and external warts; it can be used during pregnancy.
- 4. **Podofilox 0.5% (Condylox)** solution for self-treatment: Apply twice daily for 3 days followed by 4 days of no therapy. This cycle may be repeated as necessary for a total of 4 cycles; not for use on vagina or cervix; contraindicated in pregnancy.
- 5. **Surgical excision and electrocoagulation or laser** may be used.
- 6. **Large, Bulky or Extensive Lesions**
 - a. General anesthesia and wire loop cautery is effective.
 - b. Topical 5-fluorouracil cream in a 1-2% concentration has been effective in the treatment of vaginal condylomata; contraindicated in pregnancy.
- 7. **Recurrence rates** are high (25% within 3 months). No therapy has been proven to eradicate HPV.

D. Partner Referral

- 1. Examination is not required.
- 2. Annual Pap smears are recommended for partners, independent of wart history.
- 3. The use of condoms may reduce transmission to partners.

II. Molluscum Contagiosum

- A. This disease is produced by a virus of the pox virus family and is spread by sexual or close personal contact.
- B. **Clinical Features.** Lesions are usually asymptomatic, multiple, and far apart with a central umbilication. Lesions can be spread by autoinoculation and last from 6 months to many years.
- C. **Diagnosis.** The characteristic appearance is adequate for diagnosis, but

128 Pubic Infections

may be confirmed by biopsy.

- D. Treatment.** Lesions are removed by sharp dermal curette, liquid nitrogen cryosurgery, or by electrodesiccation.

III. Pediculosis Pubis (Crabs)

A. Clinical Features

1. Phthirus pubis is a blood sucking louse that is unable to survive more than 24 hours off the body.
2. It is often transmitted sexually and is principally found on the pubic hairs.
3. Severe itching may lead to excoriations and secondary bacterial infection.
4. In long-standing cases, nonblanching, blue-gray macules, averaging 0.5-1.0 cm, may appear on the abdomen and flanks.
5. **Diagnosis** is confirmed by locating nits or adult lice on the hair shafts.

B. Treatment

1. 5% permethrin cream (Elimite) is the most effective treatment; is applied for 10 minutes and washed off.
2. Kwell shampoo, lathered for at least 4 minutes, can be used; contraindicated in pregnancy or lactation.
3. All contaminated clothing and linen should be laundered.

IV. Pubic Scabies

- A.** This highly contagious infestation is caused by the *Sarcoptes scabiei*, which varies in length from 0.2-0.4 mm.

- B.** The infestation is transmitted by intimate contact or by infested clothing.

C. Clinical Features

1. The female mite burrows into the skin, and after 1 month, severe pruritus develops
2. A multifiform eruption may develop, characterized by papules, vesicles, pustules, urticarial wheals, and secondary infections on the hands, wrists, elbows, belt line, buttocks, genitalia, and outer feet.

- D. Diagnosis** is confirmed by visualization of burrows and observation of parasites, eggs, larvae, or red fecal compactions under microscopy.

E. Treatment

1. Kwell cream or lotion is applied from the neck down for 8-12 hours (contraindicated in pregnancy or lactation).
2. In infants, children under 10, in pregnant or lactating women, crotamiton 10% (Eurax) is applied to the entire body from the neck down nightly for 2 nights and washed off 24 hours after the second application.

References: See page 148.

Urologic Disorders

Benign Prostatic Hyperplasia

The prostate normally grows larger as men age. After age 40, benign prostatic hyperplasia commonly develops. BPH affects half of men by age 60, and at least 80% by age 80. Forty percent of 80 year old men will have had a prostatectomy.

Benign prostatic hyperplasia is a nonmalignant neoplasm of the prostate. It is not a precursor or predisposing factor to prostate cancer. BPH is the most common cause of obstructive or irritative voiding symptoms in elderly men.

I. Pathophysiology

- A. Prostatic stromal tissue is controlled by the adrenergic nervous system. Alpha-1 receptors control 80% of the activity of prostatic smooth muscle cells, causing contraction of the stromal component of the prostate.
- B. Many men with palpably enlarged prostates are not symptomatic while some patients with small prostates have significant voiding symptoms or urinary retention.
- C. Obstruction forces the bladder to generate higher pressures than normal to achieve micturition. Increased muscle mass in the bladder leads to reduced bladder elasticity and compliance, which manifest as a reduction in bladder capacity.
- D. If the obstruction is not relieved, bladder smooth muscle begins to be replaced by connective tissue, leading to bladder failure. This process produces the classic obstructive voiding symptoms of hesitancy, intermittency, decreased force of the stream, postvoid dribbling, and a feeling of incomplete bladder emptying.

II. Clinical Evaluation of Benign Prostatic Hypertrophy

- A. The workup for benign prostatic hypertrophy includes a history, a digital rectal examination, and a prostate-specific antigen (PSA) blood test in men older than 50 years.

Symptoms of Prostatism

Irritative Symptoms

Nocturia
Urinary frequency
Urinary urgency
Dysuria
Incontinence

Obstructive Symptoms

Decreased force of stream
Urinary hesitancy
Terminal dribbling
Double voiding
Straining to urinate

- B. **Prostate cancer** is suggested by a prostate nodule or a hardened area of the prostate on the digital rectal examination; the PSA level is usually elevated.
- C. **A urinalysis** should be obtained to exclude urinary tract infection.
- D. **Prostate Specific Antigen:** The normal range is 0 to 4. A PSA level of 4 to 10, although elevated, is statistically most likely to represent benign prostatic hypertrophy. If the examination and PSA level are normal, prostate cancer can safely be excluded.
- E. **Differential Diagnosis**
 1. The symptoms of BPH are not specific for prostate cancer because symptomatic and asymptomatic older men have the same rate of prostate cancer.
 2. The most common nonobstructive cause of obstructive voiding symptoms is diabetes mellitus. Diabetes leads to peripheral neuropathy, including the bladder nerves. Patients lose sensation and then, due to overdistension of the bladder, develop detrusor muscle failure, resulting

130 Benign Prostatic Hyperplasia

in obstruction. Glucose will be present on the urinalysis.

3. Urinary tract infection can mimic the irritative symptoms of BPH; however, pyuria will be present on urinalysis.
4. Hematuria is usually caused by BPH in older men, but urologic referral for cystoscopy may be required to rule out bladder cancer.
5. **Drugs That May Exacerbate Prostatism:** Alcohol, caffeine, first-generation antihistamines (cold remedies), tricyclic antidepressants, and urinary anti-spasmodic agents.

F. Complications of Benign Prostatic Hypertrophy

1. **Urinary tract infection** is one of the most frequent complications; can be recurrent or cause sepsis.
2. **Severe obstruction and hydronephrosis** may cause uremia that is manifest by malaise and nausea.
3. **Urinary retention** (200 to 300 mL post-voided residual urine) may present as abdominal pain with suprapubic pressure or suprapubic fullness.

III. Treatment of Benign Prostatic Hyperplasia

A. Patients with moderate symptoms should begin medical treatment.

B. Severe symptoms may warrant initiation of medical treatment, but eventually surgical intervention will usually be required.

C. Medical Therapy

1. Most patients with BPH can be treated based on symptoms, but if PSA or UA are abnormal or if a prostate nodule is detected, then a urological evaluation is mandatory.

2. Alpha-1-adrenergic Receptor Blockers

- a. Alpha-1 blockers relax the stromal (smooth muscle) component of the prostate, decreasing bladder outlet obstruction.
- b. Alpha-blockers are the drugs of choice for BPH because they are effective and because they begin to work immediately. Men with hypertension and benign prostatic hypertrophy may be able to control both problems with only one medication.
- c. Long-acting and alpha-1 specific blockers are preferable to short-acting ones because of improved patient compliance and fewer side effects.
- d. **Terazosin (Hytrin)**, 5-10 mg qd, and **doxazosin (Cardura)**, 2-8 mg qd, are long-acting alpha-1-blockers; once a day dosing is convenient.
- e. **Prazosin (Minipress)** is a short-acting alpha-1-blocker. Its main advantage is that it is inexpensive; 1-2 mg bid.
- f. The main side effects of alpha-blockers are dizziness (10%) and postural hypotension (7%), especially after the first dose. However, these side effects are usually mild and are mostly seen in patients with a history of hypertension. Normotensive patients may experience fatigue (7%).
- g. The incidence and severity of these side effects can be decreased by bedtime administration.
- h. Alpha blockers are more effective in relieving symptoms than finasteride, and the combination of alpha-blockers and finasteride is not more effective than alpha blockers alone.

3. Hormonal Manipulation

- a. **Finasteride (Proscar)** is an antiandrogen and 5-alpha reductase inhibitor that blocks prostatic conversion of testosterone to dihydrotestosterone, resulting in prostate shrinkage.

(1) 5 mg per day.

(2) Finasteride requires about 3-6 months to produce results, and clinical improvement is modest in most men, with only 33-50% reporting clinical improvement.

(3) Finasteride is used primarily for men with significant cardiac disease who can not tolerate alpha-1 blockers. It is most

effective in patients with larger prostate glands (>40 gms).

IV. Surgical Therapy

A. Transurethral Resection of the Prostate

1. TURP is the most effective way to relieve symptoms of prostatism.
2. Good resolution of urinary symptoms is achieved in 80-90%.
3. The total morbidity from TURP is about 18%; impotence occurs in 10%. Most men develop retrograde ejaculation and report a "change" in orgasm, 3% report chronic incontinence, 5% become infected, and 1% die.
4. Twenty-five percent require repeat TURP within 10 years.
5. **Definite indications for Surgery.** Urinary retention, increased creatinine, recurrent urinary tract infections, and bladder stones.
6. **Relative indications for Surgery:** Recurrent gross hematuria, severe symptoms (96% improve).

References: See page 148.

Prostatitis and Prostatodynia

I. Acute Bacterial Prostatitis

- A. Acute bacterial prostatitis** is characterized by abrupt onset of fever and chills with symptoms of urinary tract infection or obstruction, low back or perineal pain, malaise, arthralgia, and myalgias. The patient appears acutely ill and is usually a younger man. Urinary retention may develop.
- B. Physical Exam:** The prostate is enlarged, indurated, very tender, and warm. Prostate massage is contraindicated because it is painful and may cause bacterial dissemination.
- C. Laboratory Evaluation**
 1. Urine reveals WBC's. Culture reveals gram-negative organisms such as *E coli* or other Enterobacteriaceae.
 2. Nosocomial infections are often associated with a Foley catheter and may be caused by *Pseudomonas*, enterococci, *S. aureus*.
 3. Imaging may be needed in severely ill patients to rule out an abscess and need for surgery.
- D. Treatment** of acute prostatitis requires 28 days of antibiotic treatment. A fluoroquinolone, such as ofloxacin is the drug of choice.
 1. Ofloxacin (Floxin) 400 mg PO/IV bid.
 2. Ciprofloxacin (Cipro) 500 mg PO bid.
 3. Norfloxacin (Noroxin) 400 mg PO bid.
 4. Trimethoprim/SMX (TMP-SMX, Septra) 160/800 mg (1 DS tab) PO bid.
 5. Doxycycline (Vibramycin) 100 mg PO bid.
- E. Extremely Ill Septic Patients with High Fever**
 1. Hospitalization for bed rest, hydration, analgesics, antipyretics, stool softeners.
 2. Ampicillin 1 gm IV q4-6h **AND** Gentamicin or tobramycin - loading dose of 100-120 mg IV (1.5-2 mg/kg); then 80 mg IV q8h (2-5 mg/kg/d) **OR**
 3. Ciprofloxacin (Cipro) 200 mg IV q12h.
 4. A Foley catheter should not be used with acute prostatitis (suprapubic drainage may be needed).

II. Chronic Bacterial Prostatitis

- A. Chronic prostatitis** is characterized by recurrent urinary tract infections, typically in older patients, perineal, low back or suprapubic pain, testicular, penile pain or discomfort, voiding dysfunction, post-ejaculatory pain, and intermittent hematospermia. Chills and fever are not present. Often symptoms are subtle.
- B. Exam:** Prostate is usually normal and nontender, but it may occasionally be enlarged and tender.

C. Laboratory Evaluation

1. Urinalysis and culture usually shows low grade bacteriuria (*E. coli* or other Gram negative Enterobacteriaceae, *Enterococcus faecalis*, *S. aureus*, coagulase negative staph).
2. Microscopic examination of express prostatic secretions reveals more than 10-15 WBC's per high-power field.

D. Long-term Treatment (16 weeks):

Infection may be difficult to eradicate.

1. A fluoroquinolone is the drug of choice.
2. Ofloxacin (Floxin) 200-400 mg PO/IV bid.
3. Ciprofloxacin (Cipro) 250-500 mg PO bid.
4. Trimethoprim/sulfamethoxazole (TMP-SMZ, Septra) 160/800 mg (1 DS tab) PO bid.
5. Doxycycline (Vibramycin) 100 mg PO bid.
6. **Suppression** is indicated if recurrent symptomatic infections: Fluoroquinolone, TMP/SMX (1 single-strength tab qd), or nitrofurantoin (100 mg qd).

III. Chronic Nonbacterial Prostatitis

- A. The most common type of prostatitis is nonbacterial. It is eight times more frequent than bacterial prostatitis.
- B. It is characterized by perineal, suprapubic or low back pain, and irritative or obstructive urinary symptoms. Symptoms and exam are similar to chronic bacterial prostatitis but with no recurrent UTI history.
- C. Cultures are sterile and show no bacteria or uropathogens. Microscopic examination reveals 10-15 WBC's per high-power field, indicating inflammation.
- D. **Treatment (2-4 week trial of antibiotics):**
 1. Tetracycline (500 mg qid), doxycycline (100 mg bid), or Erythromycin (500 mg qid) may relieve symptoms.
 2. Irritative symptoms may respond to nonsteroidal anti-inflammatory agents, muscle relaxants, anticholinergics, hot sitz baths, normal sexual activity, regular mild exercise, and avoidance of spicy foods and excessive caffeine and alcohol.
 3. Serial prostatic massage may be helpful if the prostate is congested.
 4. The disorder is usually self-limited. In persistent cases, carcinoma of the prostate, urinary bladder and interstitial cystitis must be excluded.

IV. Prostatodynia

- A. Symptoms are similar to prostatitis, but there are no objective findings suggesting that symptoms arise in the prostate gland. Age ranges between 22-56 years.
- B. Symptoms include a wide variety of pain or discomfort in the perineum, groin, testicles, penis and urethra, or other prostatitis symptoms. Irritative or obstructive voiding symptoms are predominant. No recurrent UTI history. Stress and emotional problems are contributing factors.
- C. Tender musculature may be found on rectal examination.
- D. **Urine:** Normal (no WBC or bacteria), sterile for uropathogens. No inflammation in the prostate gland and no urinary tract infection.
- E. **Testing:** Formal urodynamic testing may detect uncoordinated voiding patterns. Cystoscopic examination may be useful.
- F. **Treatment**
 1. Alpha-adrenergic blocking agents (terazosin 1-5 mg qd, and doxazosin 1-4 mg qd) can be used to relax the bladder neck sphincter. Muscle-relaxing agents such as diazepam (Valium 2-10 mg tid) may provide relief.
 2. Nonsteroidal anti-inflammatory agents, sitz baths, normal sexual activity, avoidance of stress, spicy foods, caffeine, and alcohol may be beneficial. Prostatic massage is of no value.

References: See page 148.

Acute Epididymorchitis

I. Clinical Evaluation of Testicular Pain

- A. History.** Epididymorchitis is indicated by a unilateral painful testicle and a history of unprotected intercourse, new sexual partner, urinary tract infection, dysuria, or discharge. Symptoms may occur following acute lifting or straining.
- B. Physical.** The epididymis and testicle are painful, swollen, and tender; scrotum may be erythematous and warm with associated spermatic cord thickening or penile discharge.
- C. Differential Diagnosis of Painful Scrotal Swelling**
 1. Epididymitis, testicular torsion, testicular tumor, hernia.
 2. Torsion is characterized by sudden onset, age <20, elevated testicle, previous scrotal pain. The epididymis will be located anteriorly on either side and there is an absence of evidence of urethritis and UTI.
 3. Epididymitis is favored by fever, laboratory evidence of urethritis or cystitis, and increased scrotal warmth.

II. Laboratory Evaluation of Epididymorchitis

- A.** Epididymorchitis is indicated by leukocytosis (left shift); UA shows pyuria and bacteriuria.
- B.** Midstream urine culture will reveal gram negative bacilli. Chlamydia and Neisseria cultures should be taken, although they are often unsuccessful. Epididymal aspirate may be indicated if there is a poor treatment response or recurrent infection.
- C. Common Pathogens**
 1. **Younger Men.** It is usually associated with sexually transmitted organisms such as Chlamydia, gonorrhea.
 2. **Older Men.** It is usually associated with concomitant urinary tract infection or prostatitis; E. coli, proteus, Klebsiella, Enterobacter, Pseudomonas.

III. Treatment of Epididymorchitis

- A.** Bed rest during acute phase; scrotal elevation with athletic supporter; ice pack, analgesics, and antipyretics. Avoid sexual and physical activity.
- B. Sexually Transmitted Epididymitis in Sexually Active Males**
 1. Ofloxacin (Floxin) 300 mg bid x 10 days **OR**
 2. Ceftriaxone (Rocephin) 250 mg IM x 1 dose **AND** Doxycycline 100 mg PO bid x 10 days
 3. Treat sexual partners.
- C. Epididymitis Secondary to Urinary Tract Infection**
 1. TMP/SMX DS bid for 10 days or ofloxacin (Floxin) 300 mg PO bid for 10 days.
- D. Alternative that will Cover Sexually Transmitted and Urinary Tract Infections**
 1. Ofloxacin (Floxin) 300 mg po bid for 10 days **AND** Doxycycline 100 gm PO bid x 10 days.
 2. Treat sexual partners.

References: See page 148.

Psychiatric Disorders

Depression

I. Evaluation of Depression

- A. Evaluation should identify characteristics of depressed mood, loss of interest in usually pleasurable activities, history of past episodes of depression. The presence of insomnia, weight loss, hallucinations, suicidal ideation and planning, or alcohol or drug abuse should be sought.
- B. **Family History.** Depression or other mood disorders, suicide, drug or alcohol abuse.
- C. **Bipolar (manic-depressive) Disorder.** Before prescribing antidepressants, determine whether the patient has ever experienced a decreased need for sleep or racing thoughts because antidepressants may trigger manic episodes.

II. DSM-IV Diagnostic Criteria for Depression

- A. At least five of the following symptoms must be present, including at least one of the first two for at least two weeks:
 1. Loss of interest or pleasure in usual activities
 2. Depressed mood
 3. Significant increase or decrease in weight or appetite
 4. Insomnia or hypersomnia
 5. Psychomotor agitation or retardation
 6. Fatigue or loss of energy
 7. Feelings of worthlessness or excessive or inappropriate guilt
 8. Diminished ability to think or concentrate; indecisiveness
 9. Recurrent thoughts of death or suicidal, with or without a specific plan.

III. Medical Conditions Mimicking Depression

- A. **Drug Intoxication.** Alcohol, barbiturates, cocaine, opiates.
- B. **Metabolic Disorders.** Diabetes, electrolyte imbalances (sodium, potassium, calcium); pernicious anemia, uremia.
- C. **Medications.** Amphetamines, antihypertensives, corticosteroids, oral contraceptives, sedatives, and hypnotics.
- D. **Neoplasms.** Brain tumors, occult lesions, pancreatic carcinoma.
- E. **Endocrinologic Disorders:** Adrenal disease, thyroid disease.
- F. **Neurologic.** Multiple sclerosis, normal-pressure hydrocephalus, Parkinson's disease, dementia, subdural hematoma.
- G. **Infections or Immunologic Disorders.** Hepatitis, HIV infection, mononucleosis, syphilis, tuberculosis, lupus erythematosus.

IV. Laboratory Evaluation of Depression

- A. CBC and blood chemistries should exclude anemia or hepatic or renal abnormalities.
- B. Thyroid-stimulating hormone level may be indicated to screen for hypothyroidism.
- C. If significant unexplained weight loss is present, occult blood testing, mammography or a Papanicolaou test (in females) to rule out malignancies should be completed. Pregnancy should be excluded.
- D. Obtain a baseline electrocardiogram if preexisting cardiac disease is present or if age is >65 years.

V. Management of Depression

A. Choosing an Antidepressant

1. Consider the pattern of depression, patient's age, suicide potential, sleep habits, and any coexistent diseases or drug treatments.
2. Determine if patient (or first-degree relative) has had a previous beneficial response to a given medication.
3. Choose a sedating drug for patients with insomnia, or an SSRI over a

tricyclic for a patient with anticholinergic sensitivity or orthostatic hypotension.

- B. All antidepressant drugs are equally effective, but have different side-effect profiles.
- C. Therapeutic response may not occur for 4-8 weeks at adequate dosage.
- D. Blood plasma levels are usually not required, but may be useful to check compliance and therapeutic levels.
- E. **Anxiety.** If depression and anxiety are present, sedating antidepressants will help to control anxiety and depression.
- F. SSRIs have comparatively benign side-effect profiles and once-daily dosing. SSRIs present less danger from overdose.

Drug	Recommended Dosage	Comments
Secondary Amine Tricyclic Antidepressants		
Class as a whole: Side effects include anticholinergic effects (dry mouth, blurred vision, constipation) and alpha-blocking effects (sedation, orthostatic hypotension). Drug hangover is common but subsides within 7-10 d. Can induce cardiac rhythmic disturbances by slowing conduction.		
Desipramine (Norpramin, generics)	100-200 mg/d, gradually increasing to 300 mg/d as tolerated. Geriatric: 25-100 mg/d [10, 25, 50, 75, 100, 150 mg]	No sedation; may have stimulant effect; best taken in morning to avoid insomnia.
Nortriptyline (Pamelor)	25 mg tid-qid, max 150 mg/d. Elderly: 30-50 mg/d [10, 25, 50, 75 mg]	Sedating
Tertiary Amine Tricyclics		
Class as a whole: Anticholinergic effects and orthostatic hypotension may be more severe than with secondary amine tricyclics.		
Amitriptyline (Elavil, generics)	75 mg/d qhs-bid, increasing to 150-200 mg/d. Elderly: 10 mg tid [25, 50, 75, 100, 150 mg]	Sedative effect precedes antidepressant effect. High anticholinergic activity.
Clomipramine (Anafranil)	25 mg/d, increasing gradually to 100 mg/d; max 250 mg/d; may be given once qhs [25, 50, 75 mg].	Relatively high sedation, anticholinergic activity, and seizure risk.
Protriptyline (Vivactil)	5-10 mg PO tid-qid; 15-60 mg/d [5, 10 mg]	Useful in anxious depression; nonsedating
Doxepin (Sinequan, generics)	50-75 mg/d, increasing up to 150-300 mg/d as needed [10, 25, 50, 75, 100, 150 mg]	Sedating. Also indicated for anxiety. Contraindicated in patients with glaucoma or urinary retention.
Imipramine (Tofranil, generics)	75 mg/d in a single dose qhs, increasing to 150 mg/d; 300 mg/d. Elderly: 30-40 mg/d [10, 25, 50 mg]	High sedation and anticholinergic activity. Use caution in cardiovascular disease.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Class as a whole: Can cause headache, nausea, sedation, anxiety, and sexual dysfunction. Useful for treating depression, mixed anxiety/depression, obsessive compulsive disorder, and panic disorder.

Fluoxetine (Prozac)	10-20 mg/d initially, taken in AM; max of 80 mg/d in 2 divided doses (morning and noon). Lower dosage in elderly [10, 20 mg; 20 mg/5 mL]	Longest half-life of any antidepressant (2-9 d). Discontinue 2 mo before a planned pregnancy. Common side effects: Anxiety, insomnia, agitation, nausea, anorgasmia, erectile dysfunction, headache, anorexia, activation of mania. Also used for obsessive-compulsive disorder.
Paroxetine (Paxil)	20 mg/d initially, given in AM; increase in 10-mg/d increments as needed to max of 50 mg/d. Elderly 10-40 mg/d [10, 20, 30, 40 mg]	Headache, nausea, somnolence, dizziness, insomnia, abnormal ejaculation, anxiety, diarrhea, dry mouth.
Sertraline (Zoloft)	50 mg/d, increasing as needed to max of 200 mg/d [50, 100 mg]	Insomnia, agitation, dry mouth, headache, nausea, anorexia, sexual dysfunction.
Nefazodone (Serzone)	Start at 100 mg PO bid, increase to 150-300 mg PO bid as needed [100, 150, 200, 250 mg].	Headache, somnolence, dry mouth, blurred vision. Postural hypotension, impotence.

Phenylethylamine

Venlafaxine (Effexor)	75 mg/d in 2-3 divided doses with food; increase to 225 mg/d as needed. Taper when discontinuing [25, 37.5, 50, 75, 100 mg].	Inhibits norepinephrine and serotonin. Side effects: hypertension, nausea, somnolence, insomnia, dizziness, abnormal ejaculation, headache, dry mouth, anxiety.
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Aminoketone

Bupropion (Wellbutrin, Wellbutrin SR)	100 mg bid; after at least 3 d, increase to 100 mg tid as needed [75, 100 mg] Sustained release: 100-200 mg bid [100, 150 mg]	Side effects: Agitation, dry mouth, insomnia, headache, nausea, constipation, tremor. Good choice for patients with sexual side effects from other agents; contraindicated in seizure disorders.
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Triazolopyridine

Trazodone (Desyrel, generics)	150 mg/d, increasing by 50 mg/d every 3-4 d 400 mg/d in divided doses [50, 100, 150, 300 mg]	Rarely associated with priapism. Orthostatic hypotension in elderly. Sedating.
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G. Tricyclic Agents

1. Side effects (especially hangover) are worst during the first month of

therapy, and usually become more tolerable afterward.

2. Early in the course a patient may sleep better, but patients rarely describe affective improvement until at least 3-4 weeks.
3. Only minimum quantities should be prescribed because of cardiotoxicity with overdose.

H. Serotonergic Agents

1. Commonly used as first-line agents as well as secondary choices for patients whose depression does not respond to tricyclics. Although many patients take SSRIs with no adverse consequences, the most frequent side effects are insomnia, agitation, and sexual dysfunction. The SSRIs tend to be nonsedating, making them a good choice for patients who are lethargic or withdrawn.
2. Sertraline or paroxetine are less energizing than fluoxetine, so these agents are better choices in depression combined with anxiety.
3. Fluoxetine can have a stimulant effect on some patients, especially early in treatment.

I. Antidepressant-Related Sexual Dysfunction

1. Antidepressants cause sexual impairment in 20-30%, especially the selective serotonin reuptake inhibitors (SSRIs), though any antidepressant may be implicated.
2. Bupropion (Wellbutrin) is a mildly stimulating antidepressant, and may be useful in patients who have had sexual impairment from other drugs. The need for multiple daily doses reduces compliance; however a sustained release formulation may be taken bid.

J. Monoamine Oxidase Inhibitors

1. Contraindications discourage common use.
2. Requires a tyramine-free diet. Risk of hypertensive crisis.

K. Electroconvulsive therapy is a safe and effective treatment; especially if high risk for suicide and insufficient time for a trial of medication.

References: See page 148.

Anxiety Disorders

I. Generalized Anxiety Disorder

- A. Generalized anxiety disorder (GAD), the most common of the anxiety disorders, is characterized by unrealistic or excessive anxiety and worry about two or more life circumstances for at least six months.
- B. Chronic worry is a prominent feature of GAD as opposed to the intermittent terror that characterizes panic disorder.
- C. Patients may report that they "can't stop worrying," which may revolve around valid life concerns including money, job, marriage, health, and safety of children.
- D. Other features of GAD include insomnia, irritability, trembling, dry mouth, and a heightened startle reflex.
- E. The presence of depression should be assessed because 30-50% of patients with anxiety disorders will also meet the criteria for major depression. Drugs and alcohol may contribute to anxiety disorders.

II. Panic Disorder

- A. Patients with panic disorder report discrete periods of intense terror and doom.
- B. **Characteristics of Panic Attacks**
 1. Dizziness, unsteadiness, light-headedness, or faintness
 2. Chest pain or discomfort
 3. Chills or hot flushes
 4. Choking sensations
 5. Derealization or depersonalization
 6. Fear of dying

7. Fear of losing control or "going crazy"
 8. Nausea or other abdominal distress
 9. Palpitations, pounding, or racing heart
 10. Sweating, trembling or shaking
 11. Paresthesias
 12. Smothering sensations or shortness of breath
- C. The panic episode generally resolves within 10-30 minutes. This first panic attack generally is precipitated by a major life event. Agoraphobia may develop, with anticipatory anxiety and phobic avoidance.
- D. Panic disorder is diagnosed only when panic attacks are unexpected and cannot be attributed to other conditions.
- E. Panic attacks may occur in posttraumatic stress disorder and social phobia, and in some medical disorders (hyperthyroidism, pheochromocytoma).

III. Medical Disorders Causing Panic-like Symptoms

- A. **Hyperthyroidism** may cause anxiety, tachycardia, palpitations, sweating, dyspnea.
- B. **Cardiac rhythm disturbances and mitral valve prolapse** may cause panic symptoms.
- C. **Substance abuse or dependence** with withdrawal symptoms may resemble panic disorder.
- D. **Pharmacologic Causes of Anxiety**
1. Analgesics (salicylate intoxication/NSAIDs)
 2. Sedatives (antihistamine intoxication/withdrawal)
 3. Sympathomimetics (phenylpropanolamine)
 4. Psychotropics (akathisia), stimulants, selective serotonin reuptake inhibitors.
 5. Large doses of caffeine may produce anxiety.
 6. Cocaine, amphetamines, theophylline, beta agonists, over-the-counter decongestants, steroids, and marijuana can cause panic attacks or anxiety.

IV. Laboratory Evaluation of Anxiety Disorders

- A. Chemistry profile (glucose, calcium and phosphate), TSH.
- B. **Special Tests.** Urine drug screen, cortisol, serum catecholamine level.

V. Treatment of Anxiety Disorders

A. Nondrug Approaches to Anxiety

1. Discontinue caffeinated beverages and avoid excess alcohol.
2. Daily exercise and adequate sleep (with the use of medication if necessary) should be advised.

VI. Drug Therapy for Anxiety Disorders

- A. Tricyclic antidepressants and SSRIs are widely used to treat panic disorder and generalized anxiety disorder. Their onset of action is much slower than that of the benzodiazepines, but they do not have addictive potential and may be more effective. An antidepressant is the agent of choice when elements of depression are present in addition to anxiety.
1. Sedating antidepressants often have an early effect of promoting better sleep, although 2-3 weeks may pass before a patient experiences an antianxiety benefit. Better sleep usually brings some relief from symptoms, and the patient's functional level begins to improve almost immediately.
 2. Anxious patients benefit from the sedating effects of imipramine (Tofranil), amitriptyline (Elavil), and doxepin (Sinequan). The daily dosage should be at least 50-100 mg.
 3. Desipramine (Norpramin) is useful if sedation is not desired. Most of the selective serotonin reuptake inhibitors (fluoxetine [Prozac]) will worsen panic symptoms before relieving them.
- B. **Benzodiazepines**
1. Benzodiazepines are used for patients with panic disorder because of the need for more rapid relief.
 2. Tolerance to the sedative effects develops, but not to the antianxiety

140 Anxiety Disorders

properties.

3. Patients with depression and anxiety should not receive anxiolytics because benzodiazepines may worsen depression.
4. Alprazolam (Xanax), diazepam (Valium), lorazepam (Ativan), and clonazepam (Klonopin) are effective for panic disorder.
5. Benzodiazepines can be used in conjunction with an antidepressant. Therapy starts with alprazolam and an SSRI or tricyclic antidepressant. Alprazolam is then tapered after 2-3 weeks, when the antidepressant has started to take effect.
6. Clonazepam (Klonopin) has an onset at about one hour and lasts about 8-12 hours, making it the better choice for around-the-clock symptom control for frequent panic or anxiety.
7. Diazepam (Valium) remains a good choice in either situational or generalized anxiety.
8. Benzodiazepines can almost always relieve anxiety if given in adequate doses. Dependency becomes a problem with use daily for more than two or three weeks. Some degree of dependency is usually manageable.
9. A withdrawal syndrome occurs in 70% of patients which includes anxiety, dysphoria, sleep and perceptual disturbances, and appetite suppression. Slow tapering of benzodiazepines is crucial.

Drug	Dosage	Comments
Benzodiazepines		
Alprazolam (Xanax)	0.25-0.5 mg tid; increase by 1 mg/d at 3-4 day intervals to 0.75-4 mg/d [0.25, 0.5, 1, 2 mg]	Intermediate onset. Least sedating drug in class. Strong potential for physiologic dependence
Chlordiazepoxide (Librium, generics)	5 mg tid; 15-100 mg/d [5, 10, 25 mg]	Intermediate onset
Clonazepam (Klonopin)	0.5 mg tid; 1.5-20 mg/d [0.5, 1, 2 mg]	Intermediate onset. Long half-life; much less severe withdrawal
Clorazepate (Tranxene, generics)	7.5 mg bid; 15-60 mg/d [3.75, 7.5, 15 mg]	Fast onset
Diazepam (Valium, generics)	2 mg bid; 4-40 mg/d [2, 5, 10 mg]	Very fast onset
Halazepam (Paxipam)	20-40 mg tid-qid; 80-160 mg/d [20, 40 mg]	Intermediate to slow onset
Lorazepam (Ativan, generics)	1 mg bid; 2-6 mg/d [0.5, 1, 2 mg]	Intermediate onset

Oxazepam (Serax, generics)	10 mg tid; 30-120 mg/d [10, 15, 30 mg]	Intermediate to slow onset
Miscellaneous		
Amitriptyline (Elavil, generics)	75 mg/d qhs-bid, increasing to 150-200 mg/d [25, 50, 75, 100, 150 mg]	Sedating, high anticholinergic activity
Buspirone (BuSpar)	10 mg bid; max 60 mg/d; increase to 10 mg tid prn [5, 10, 15 mg dividose]	Antidepressant; nonaddicting, nonsedating. Not for prn usage; requires 2-3 wk to become effective.
Doxepin (Sinequan, generics)	75 mg qhs or bid, max 300 mg/d [10, 25, 50, 75, 100, 150 mg]	A tricyclic antidepressant with antianxiety effects.

C. Buspirone (BuSpar)

1. Buspirone is a nonbenzodiazepine anxiolytic. It is most effective for generalized anxiety in patients who have never taken benzodiazepines. Buspirone requires 2 weeks to become effective, and it may not improve sleep. It is unlikely to cause dependence, and it has some antidepressant effects.
2. Combined therapy with a benzodiazepine and buspirone may be used for anxiety, with subsequent tapering of the benzodiazepine.

D. Beta Blockers

1. Propranolol HCL (Inderal) and other beta-blockers are very effective for performance anxiety or social phobia, but they can provoke depression.
2. Dosage can be quite low (propranolol 20 mg bid), or it can be used as needed, 1 hour before anticipated stress.

References: See page 148.

Insomnia

I. Causes of Insomnia

- A. Transient Insomnia** is the most common form of insomnia, and it is often caused by factors such as stress, attempting to sleep in a new place, changes in time zones, or changing bedtimes due to shift work.
- B. Chronic Insomnia** is commonly caused by depression, anxiety disorders and substance abuse.
- C. Medical Disorders** can cause insomnia because of pain, nausea, dyspnea, cough, gastroesophageal reflux, sleep apnea, and myoclonus.
- D. Drugs Associated with Insomnia.** Antihypertensives, caffeine, diuretics, oral contraceptives, phenytoin, selective serotonin reuptake inhibitors, protriptyline (Vivactil), corticosteroids, stimulants, theophylline, thyroid hormone.

II. Psychiatric Illnesses Associated with Insomnia

- A. Depression** is the most common psychiatric diagnosis associated with insomnia. Depression often develops in patients with chronic insomnia.

- B. Chronic Anxiety.** 10% of chronic insomnia is secondary to generalized anxiety or panic disorder. Chronic use of long-acting benzodiazepines may be indicated for these patients.

III. Behavioral Management of Insomnia

- The patient should go to bed only when sleepy.
- The bed should be used for sleeping only. Reading, watching TV, or eating in bed should be discouraged.
- If unable to sleep, the patient should move to another room, stay up until sleepy, then return to bed.
- The patient should set the alarm and get up at the same time every morning, regardless of how well he slept during the night.
- Naps and caffeinated beverages should be eliminated.

IV. Pharmacotherapy of Insomnia

- Hypnotics should be given for only a limited time, usually less than two to four weeks.
- Sedating antidepressants, such as doxepin (Sinequan), trazodone (Desyrel), or amitriptyline (Elavil), can also be used to treat insomnia and are especially useful when the patient has underlying depression.
- If benzodiazepines are used, patients with initial difficulty in falling asleep will benefit from a short-acting agent like zolpidem (Ambien). Patients who have early morning insomnia will need a longer acting agent such as estazolam (ProSom).
- Effects of Benzodiazepines on Sleep.** Slow wave sleep and rapid eye movement (REM) sleep are reduced; REM sleep latency is prolonged. REM sleep and slow wave sleep have important functions in learning, memory, and adaptation to stress.
- Long-acting Benzodiazepines** generally are not suitable for insomnia, but may be useful in treating insomnia that is associated with chronic anxiety.
- Zolpidem (Ambien)** is a nonbenzodiazepine, although it acts on the benzodiazepine receptor.
 - It has a minimal effect on sleep stages and promotes a more natural sleep.
 - Zolpidem has a rapid onset of action, lacks withdrawal effects or rebound insomnia and causes little or no tolerance.
 - No impairment of performance is evident during the day.

Sedative-Hypnotic Benzodiazepines

Drug	Dosage	Half-life (hrs)	Side Effects	Positive Effects
Flurazepam (Dalmane)	15-30 mg [15, 30 mg]	48-120	Daytime drowsiness, confusion; sedative interactions. Intermediate- to long-acting.	Suppresses daytime anxiety; relative lack of withdrawal.
Triazolam (Halcion)	0.125-0.5 mg [0.125, 0.25 mg]	2-6	Amnesia; confusion; rebound insomnia; Abrupt onset and offset of action. Side effects can be unpredictable.	Short duration results in less daytime sedation.

Temazepam (Restoril)	15-30 mg [7.5, 15, 30 mg]	8-20	Rebound insomnia. Has slowest onset (30-60 min)	Daytime alertness after use. Short- to intermediate-acting.
Estazolam (ProSom)	1-2 mg [1, 2 mg]	8-24	REM sleep suppression; withdrawal symptoms. Daytime sedation	Short- to intermediate-acting.
Quazepam (Doral)	15 mg [7.5, 15 mg]	48-120	Daytime drowsiness, confusion; sedative interactions. Intermediate- to long-acting.	Lack of withdrawal effects; daytime alertness after use. Intermediate- to long-acting.
Zolpidem (Ambien)	10 mg; 5 mg in elderly [5, 10 mg]	3-8	Potential for idiosyncratic side effects. Short acting.	Daytime alertness after use; lack of withdrawal; no suppression of REM.

References: See page 148.

Index

- 3TC 32
 Acarbose 78
 Accolate 24
 Accupril 13, 18
 Accutane 88
 Acebutolol 9
 Acne Rosacea 91
 Acne vulgaris 87
 Acular 23
 Acyclovir 38, 40
 Adalat-CC 19
 AeroBid 24, 25
 Aeromonas 54
 Afrin 23
 AGUS 102
 AIDS 31
 Albuterol 24
 Alendronate 117
 Aleve 83, 107, 108
 Allegra 22
 Allergic Rhinitis 21
 Alomide 24
 Alopecia Areata 91
 Alprazolam 109, 140
 Altace 18
 Alupent 24, 25
 Alzheimer's Disease 66
 Amaryl 78
 Ambien 142, 143
 Aminonide 98
 Amebiasis 54
 Amenorrhea 109
 Amiloride-hydrochlorothiazide 17
 Amitriptyline 60, 136, 141
 Amlodipine 10, 19
 Amoxicillin 30, 48
 Amoxicillin/clavulanate 25, 28, 30, 31, 36, 97
 Amoxil 30
 Ampicillin 34, 36, 131
 Ampicillin/Sulbactam 28
 Anafranil 136
 Anaprox 58, 83, 107, 108, 120
 Ancef 36
 Androgen Insensitivity Syndrome 112
 Androgen Secreting Neoplasms 112
 Angina 7
 Anorectal Manometry 50
 Anovulation 111
 Antazoline 23
 Anti-Leukotrienes 24
 Antibiotic-Related Diarrhea 52
 Antiretroviral Therapy 32
 Antivert 62
 Antrectomy 49
 Anxiety Disorders 138
 Aortic Coarctation 15
 Aricept 67
 Aristocort 90
 Arrhythmias 62
 ASCUS 102
 Asherman syndrome 112
 Aspercreme 40
 Astemizole 22
 Asthma 24
 Atenolol 9, 18, 60
 M19
 Ativan 140
 Atopic Dermatitis 89
 Atorvastatin 72
 Atrophic Vaginitis 116, 127
 Attapulgit 54
 Atypical Glandular Cells 102
 Atypical Squamous Cells 102
 Augmentin 25, 28, 30, 31, 36, 97
 Aura 63
 Axid 45
 Acid Pulvules 48
 Azelaic Acid 88
 Azelex 88
 Azithromycin 25, 28, 30, 97, 124
 Azmacort 24, 25
 AZT 32
 Bacitracin 44
 Back Pain 81
 Bacterial Vaginosis 124
 Bactrim 30
 Bactroban 97
 Basal Caloric Requirement 77
 Beclomethasone 23-25, 30
 Beclovent 24, 25
 Beconase 23, 30
 Belsey Procedure 46
 Benazepril 18, 19
 Benemid 122
 Benign Positional Vertigo 60, 62
 Benign Prostatic Hyperplasia 129
 Benoxyl 87
 Benzagel 87
 Benzamycin 88
 Benzathine penicillin 31
 Benzoyl Peroxide 87
 Bepridil 10
 Berotec 24
 Betamethasone 98
 Betamethasone dipropionate 90, 98
 Betaxolol 9
 Biaxin 25, 28, 30, 31, 48
 Bicillin 31, 41
 Biguanides 78
 Bile Acid Sequestrants 70, 71
 Bilroth I 49
 Bilroth II 49
 Bismuth 47
 Bisoprolol 9
 Bisphosphonates 117
 Bitolterol 24
 Bleph-10 44
 Blocadren 9, 18
 Bone Mineral Density Testing 117
 Breakthrough Bleeding 104
 Breast Disorders 113
 Breast Pain 113
 Brevicon 105
 Bromocriptine 109
 Budesonide 23, 30
 Bumetanide 13
 Bumex 13
 Bupropion 137
 BuSpar 109, 141
 Buspirone 141
 Butoconazole 125
 Butorphanol 59
 Cafergot 58
 Calan SR 10, 19
 Calcipotriene 98
 Calcitonin 117
 Calcium 116
 Calcium carbonate 117, 118
 Campylobacter jejuni 54
 Candida Vulvovaginitis 125
 Cantharone 91
 Capoten 13, 18
 Capsaicin 40, 76
 Captopril 13, 18
 Carafate 48
 Carbamazepine 64, 65
 Carbuncles 96
 Cardene-SR 19
 Cardizem CD 10, 19
 Cardizem SR 10, 19
 Cardura 19, 130
 Carisoprodol 84
 Carteolol 18
 Cartrol 18
 Carvedilol 9, 14
 Cauda Equina Syndrome 81
 Cefadroxil 36, 94
 Cefazolin 36
 Cefixime 25, 30, 36, 123
 Cefixox 28, 36
 Cefotan 123
 Cefotaxime 28, 123
 Cefotetan 123
 Cefoxitin 122, 123
 Cefpodoxime 28, 30
 Cefazidime 36
 Ceflin 25, 28, 30
 Ceftriaxime 36, 123
 Ceftriaxone 122, 123, 133
 Cefuroxime 28
 Cefuroxime axetil 25, 28, 30
 Celiac Disease 55
 Cellulitis 97
 Cephalixin 31, 94, 97
 Cephalothin 36
 Cetirizine 22
 Chemoprophylaxis 43
 Chlamydia Trachomatis 124
 Chlordiazepoxide 140
 Chlorothiazide 17
 Chlorthalidone 17
 Cholesterol 69
 Cholestyramine 71
 Chronic Diarrhea 54
 Chronic Obstructive Pulmonary Disease 25
 Chronic Prostatitis 131
 Ciloxan 44
 Cimetidine 45, 48
 Clomipramine 136
 Clorazepate 140
 Clotrimazole 126
 Cipro 34, 36, 53, 123, 131, 132
 Ciprofloxacin 34, 36, 44, 53, 123, 131, 132
 Cisapride 46
 Claforan 28
 Clarithromycin 25, 28, 30, 31, 48
 Claritin 22
 Cleocin 34, 122, 123, 125
 Cleocin-T 88
 Climacteric Syndromes 114
 Clindamycin 88, 122, 123, 125
 Clobetasol 90, 98
 Clonazepam 140
 Clostridium difficile 52, 54
 Clotrimazole 93-95, 126
 Cognex 67
 Colace 51
 Colestid 71
 Colestipol 71
 Collis Gastroplasty 46
 Colonic transit scintigraphy 50
 CoLyte 51
 Combivent 24
 Compazine 62
 Condylox 91, 127
 Congestive Heart Failure 11
 Conjugated estrogens 115
 Conjunctivitis 21
 Constipation 49
 Contact dermatitis 89
 Contraception 103
 Contraceptive Implants 105
 Contraceptives 103
 Cordran 98

Coreg 9, 14	DynaCirc 19	Foscavir 40
Corgard 9, 18	Dysplasia 102	Fosinopril 18
Coronary Artery Disease 7	E coli 0157:H7 53	FSH 115
Covera-HS 19	Echocardiography 7	Functional Diarrhea 55
Crabs 128	Econazole 93, 95	Furosemide 13
Crixivan 32	Eczema 89	Furuncles 96
Crolom 23	EES31	Gabapentin 65
Cromoglycate 23	Effexor 137	Gamma benzene hexachlo- ride 91
Cromolyn 23, 24	Elavil 60, 136, 141	Garamycin 44, 123
Crotamiton 128	Electroencephalogram 64	Gastric Ulcer 49
Cryotherapy 90	Electromyograph 50	Gastroduodenostomy 49
Cryptosporidiosis 54	Electromyography 85	Gastroesophageal reflux dis- ease 45
Cushing's Syndrome 16, 112	Elimate 91, 128	Gastrojejunostomy 48, 49
Cyclobenzaprine 84	Elixophyllin 24	Generalized Anxiety Disorder 138
Cystic hyperplasia 121	EMLA 40	Gentamicin 34, 44, 123, 131
Cytotec 84	Enalapril 13, 18, 19	Giardiasis 54
d4T 32	Endometrial Ablation 121	Glimepiride 78
Dalmane 142	Endometrial hyperplasia 121	Glipizide 78
Danazol 109	Endometrial Sampling 120	Glucophage 78
Dapsone 32	Endometriosis 107	Glucotrol 78
DDC 32	Engerix B 33	Glyburide 78
DDI32	Enoxacin 123	Glycosylated hemoglobin 73
Decadron 90	Enterohemorrhagic E coli 54	Glynase PresTab 78
Defecography 50	Enteropathogenic E coli 54	GnRH agonist 107
Dehydroepiandrosterone sulfate 112	Entex 23	GoLyte 51
Delavirdine 32	Epididymorchitis 133	Gonorrhea 123
Delirium 66	Epilepsy 63	Griseofulvin 94, 95
Demadex 13	Epivir 32	Groin Rashes 93
Dementia 66	Ergotamine 58, 59	Gyne-Lotrimin 126
Depakote 60, 65	Erycette 88	Habitrol 26
Depression 135	Erythema Multiforme 92	Halazepam 140
Dermatitis 89	Ery thromycin 28, 31, 44, 90, 94, 97	Halcinonide 98
Dermatology 87	Erythromycin ethyl succinate 31	Halcion 142
Dermatophytosis 95	Erythromycin solution 88	Hallpike Maneuver 60
Desipramine 60, 136	Erythromycin-sulfisoxazole 30	Halobetasol 90
Desogen 104	Esgic 58	Halog 98
Desquam-X 87	Estazolam 143	Hb A1c 74
Desyrel 137	Estrogen 115, 117	HCTZ 17, 19
DEXA 117	Ethambutol 42	HDL-cholesterol 69
Dexamethasone 90	Ethosuximide 65	Headache 57
DHE 59	Etodolac 83	Heart Failure 11
DiaBeta 78	Etreinate 98	Helicobacter pylori 47
Diabetes 72, 76	Eurax 128	Herpes simplex 37
Diabetic Diarrhea 55	Exercise testing 7	Herpes Zoster 39
Diarrhea 52	Exudative Diarrhea 55	HGSIL 102
Diazepam 62, 140	Famciclovir 38, 40	Hill Procedure 46
Dichloralphenazone 58	Famotidine 45, 48	Hismanal 22
Dicloxacillin 31, 90, 94, 96, 97	Famvir 38, 40	HIV 31
Didanosine 32	Fe brile Dysenteric Syndrome 53	Hivid 32
Diflorasone 90	Felbamate 65	HMG CoA Reductase Inhibi- tors 71
Diflucan 93, 94, 126	Felbatol 65	Hormone Replacement Ther- apy 115, 117
Diflunisal 83	Feldene 83	Hot Flashes 114
Digoxin 13, 14	Felodipine 10, 19	Humalog 74
Dihydroergotamine 59	Femstat 125	Human Papilloma Virus 127
Dilantin 65	Fenoterol 24	Hydrochlorothiazide 17
Dilatrate-SR 9	Fexofenadine 22	Hydrocortisone 90, 98
Diltiazem CD 10	Fiberall 50	HydroDiuril 17
Diltiazem SR 10, 19	FiberCon 50	Hygroton 17
Diphenoxylate 54	Fibrocystic Complex 114	Hyperaldosteronism 16
Diprolene 90, 98	Finasteride 130	Hyperandrogenic Chronic Anovulation 112
Diuril 17	Fioricet 58	Hypercholesterolemia 70
Diverticulitis 33	Fiorinal 58	Hyperkeratosis 102
Dizziness 62	Fiorinal w/codeine 58	Hyperlipidemia 69
DMPA 105	Fla gyl 34, 47, 53, 122, 125, 126	Hyperparathyroidism 16
Dobutamine 14	Fleet 51	Hyperprolactinemia 110
Dobutrex 14	Flexeril 84	Hypertension 15
Docusate 51	Flonase 23, 30	Hypertriglyceridemia 72
Dolobid 83	Florone 90	Hypothalamic Dysfunction 111
Donepezil 67	Flovent 24, 25	Hytrin 19, 130
Doral 143	Flo xin 36, 53, 122-124, 131-133	Hyzaar 19
Dovonex 98	Fluconazole 93, 94, 126	Ibuprofen 58, 83, 107, 120
Doxazosin 19, 132	Flunisolide 23-25, 30	Imdur 9
Doxepin 136, 141	Fluocinolone 98	Imipenem/Cilastatin 28, 37
Doxycycline 25, 28, 41, 122-124, 131-133	Fluoxetine 109, 137	Imipramine 136
Drug Eruptions 92	Flurandrenolide 98	Imitrex 59
Duodenal Ulcer Disease 48	Flurazepam 142	
Duofilm 91	Fluticasone 23, 25, 30	
Duricef 36, 94	Fluvastatin 72	
Dyazide 17	Fortaz 36	
Dycill 97	Fosamax 117	
	Foscarnet 40	

Immunotherapy 24	Low back pain 81		Nelfinavir 32
Imodium 54	Low-Grade Intraepithelial	Squamous Lesions	Neo-Synephrine 23,31
Impetigo 96	102		Nephropathy 76,80
Indapamide 17	LSIL 102, 103		Neurontin 65
Inderal 9,18,60	Macroductin 36		Neuropathy 76,81
Inderal LA 18,60	Mastodynia 114		Neurosyphilis 41
Indinavir 32	Maxair 24		Nevirapine 32
Infectious conjunctivitis 43	Maxaquin 36		Niacin 70,71
INH 43	Maxzide 17		Nicardipine SR 19
Injectable Contraception 105	Meclizine 62		Nicoderm 26
Injectable Depot Medroxyprogesterone 105	Mediplast 90		Nicorette 26
Insomnia 141	Medrol 24,25		Nicotine nasal spray 25
Insulin 73,74,79	Medroxyprogesterone 107, 111, 115,117		Nicotine Polacrilex 26
Insulin Lispro 74	Mefenamic acid 58, 107, 108, 119		Nicotine transdermal 26
Insulin-dependent diabetes 72	Mefoxin 122, 123		Nicotinic Acid 71
Intal 24	Meniere's Disease 61,62		Nicotrol NS 25
Intrauterine Adhesions 112	Menopause 114		Nifedipine XL 10,19
Intrauterine Device 106	Metamucil 50		Nipple Discharge 113
Invirase 32	Metaprel 24		Nissen Fundoplication 46
ISMO 9	Metaproterenol 24		Nitrates 8
Isometheptene 58	Metformin 78		Nitrofurantoin 36
Isoniazid 42	Methocarbamol 84		Nitroglycerin Patches 8
Isoptin SR 10	Methotrexate 98		Nitroglycerine 8
Isordil 9	Methylprednisolone 25		Nitrolingual 8
Isordil Tembids 9	asthma 24		Nitrostat 8
Isosorbide 9	Metocorten 24		Nizatidine 45,48
Isosorbide Dinitrate 9	Metoclopramide 45		Nizoral 93-95, 126
Isosorbide Mononitrate 9	Metoprolol 9, 14, 18,60		Non-Nucleoside Reverse Transcriptase Inhibitors 32
Isotretinoin 88	Metoprolol XL 18		Nonbacterial prostatitis 132
Isradipine 19	MetroGel 125		Norfloracin 36, 44, 53, 123, 131
Itraconazole 93-95, 126	Metronidazole 34, 47, 48, 53, 122,125,126		Noroxin 36,53,131
IUD 106	Metronidazole gel 125		Norplant II 105
Kaopectate 54	Mevacor 72		Norplant VI 105
Keflex 31,36,94,97	Miacalcin 117		Norpramin 60,136
Kenalog 90	Micatin 93-95		Nortriptyline 60,136
Kerlone 9	Miconazole 93-95,125		Norvasc 10,19
Ketoconazole 93-95, 126	Microalbuminuria 76,80		Norvir 32
Ketoprofen 58,83	Micronase 78		NPH Insulin 74
Ketorolac 23,58,83	Midrin 58		Nuprin 120
Klonopin 140	Mifepristone 106		Nystatin 93
Kwell 91,128	Milrinone 14		Obstructive Defecation 50
Lactulose 51	Mineral oil 51		Occlusal 91
Lamictal 65,66	Minipress 19,130		OcuClear 23
Lamisil 93,94	Minocin 88		Ofloracin 36, 53, 122-124, 131-133
Lamivudine 32	Minocycline 88		Omeprazole 46,48
Lamotrigine 65,66	Misoprostol 84		Oral Contraceptives 103
Lansoprazole 46,48	Modicon 105		Ortho Tri-Cyclen 104
Lasix 13	Moduretic 17		Ortho-Cept, 104
LDL-cholesterol 69	Moexipril 18		Ortho-Cyclen 104
Lescol 72	Molluscum Contagiosum 127		Ortho-Novum 104, 120
Leukotriene-Receptor Antagonist 24	Monistat 7 125		Ortho-Novum 7/7/7 104
Leuprolide 107	Monoket 9		Orthoceph 105
Levaquin 36	Monopril 18		Orthostatic Hypotension 61
Levocabastine 23	Motion Sickness 61		Orudis 58,83
Levofloxacin 36	Motrin 58,83, 107, 120		Oruvail 83
Librium 140	Mupirocin 97		Osmotic Diarrhea 55
Lightheadedness 62	Mycobacterium Avium Complex 33		Osteoarthritis 81
Lipitor 72	Mycostatin 93		Osteoporosis 115,116
Lisinopril 13,18	Nabumetone 83		Ovarian Failure 111
Lispro 74	Nadolol 9,18		Ovcon 105
Livostin 23	Nafarelin 107		Ovral 106
Lo/Ovral 105	Naftifine 93		Ovulation Suppression 109
Lodine 83	Naftin 93		Oxazepam 141
Lodoxamide 24	Nail Fold Lesions 93		Oxiconazole 93
Loestrin 104	Nail Plate Infections 94		Oxistat 93
LoEstrin 104,105	Naph-con-A 23		Oxy-10 87
Lomefloxacin 36,123	Naphazoline 23		Oxymetazoline 23
Lomofil 54	Naphcon 23		Oxymetazoline (Afrin) 23
Loperamide 54	Naprosyn 83,107,108,120		Pamelor 60,136
Lopressor 9,14,18,60	Naproxen 83,107,108,120		Panic Attacks 138
Lorabid 25,28,30	Naproxen sodium 58, 83, 107, 108		Panic Disorder 138
Loracarbef 25,28,30	Nasacort 23,30		Pap smear 101
Loratadine 22	Nasalacrom 23		ParaGard 106
Lorazepam 140	Nasalide 23,30		Parakeratosis 102
Losartan 19	Nedocromil 24		Parlodel 109
Lotensin 18,19	Nefazodone 137		Paromomycin 54
Lotrel 19			Paronychia 93
Lotrimin 93-95			Paronychias 93
Lovastatin 72			

Paroxetine 137	Prozac 109, 137	Stable Angina 7
Pathocil 96, 97	Pruritus Ani 98	Stadol 59
Paxil 137	Pseudodementia 66	Statins 70, 71
Paxipam 140	Pseudoephedrine 23	Stavudine 32
PCP prophylaxis 32	Pseudomembranous colitis. 52	Steven's Johnson syndrome 93
Pedialyte 53	Psoriasis 97	Streptococcal pharyngitis 31
Pediazole 30	Psyllium 70	Stress testing 7
Pediculosis Pubis 128	Public Infections 127	Sucralfate 48
Pe lvic Inflammatory Disease 121	Purified protein derivative 42	Sudafed 23
Penicillin benzathine 31	Pyelonephritis 35	Sulamyd 44
Penicillin G benzathine 41	Pyloprost 48	Sulfacetamide 44
Penicillin V 31	Pyrazinamide 42	Sulfonylureas 78
Pentamidine 32	Pyridium 36	Sumatriptan 59
Pentoxifylline 76	Quazepam 143	Superficial Folliculitis 96
Pepcid 45, 48	Questran 71	Suprax 25, 30, 36, 123
Peptic ulcer disease 47	Quinacrine 54	Synalar 98
PeptoBismol 47	Quinapril 13, 18	Syphilis 41
Permethrin 91, 128	Radionuclide angiography 7	T Cu 380A 106
Persa-Gel 87	Ramipril 18	Tacrine 67
Pharyngitis 31	Ranitidine 45, 47, 48	Tagamet 45, 48
Phenazopyridine 36	Ranitidine-bismuth-citrate 48	Technetium 8
Pheniramine 23	Reflexes 82	Tegison 98
Phenobarbital 65	Reglan 45	Tegretol 64
Phenylephrine 23	Rehydration 53	Temazepam 143
Phenylpropanolamine 23	Relafen 83	Temovate 90, 98
Phenylpropanolamine (Entex) 23	Renovascular Hypertension 16	Tenormin 9, 18, 60
Phenytoin 65	Renovascular Stenosis 16	Terazol 7 125
Pheochromocytoma 15, 16	Restoril 143	Terazosin 19, 130, 132
Phthirus pubis 128	Retin A 87	Terbinafine 93, 94
Pindolol 18	Retinopathy 75, 80	Terbutaline 24
Piperacillin/tazobactam 28, 36	Retrovir 32	Terconazole 125
Pirbuterol 24	Rezulin 80	Testicular feminization syndrome 112
Piroxicam 83	Rhinacort 23, 30	Testicular Pain 133
Pityriasis rosea 95	Ricelyte 53	Testosterone 112
Plendil 10, 19	Rifamate 42	Tetanus Ig 43
Plesiomonas 54	Rifampin 42	Tetanus prophylaxis 43
Pneumonia 27	Ritonavir 32	Tetanus toxoid 43
Podoflox 91, 127	Robaxin 84	Tetracycline 41, 47, 88
Podophyllin 127	Rocephin 122, 123, 133	Theo-Dur 24, 25
Polycystic Ovarian Syndrome 112	Rotavirus 53	Theophylline 24, 25
Ponstel 58, 107, 108, 119	RU486 106	Ticarillin/clavulanate 28, 37
Postcoital Contraception 106	Rynacrom 23	Tilade 24
Postexposure Prophylaxis 32	Saline Wet Mount 124	Timentin 28, 37
Postherpetic Neuralgia 40	Salmeterol 24	Timolol 9, 18
Potassium Hydroxide 124	Salmonella 54	Tinea 95
PPD 42	Saquinavir 32	Tinea Unguim 95
Pravachol 72	Scabies 91, 128	Tinea Versicolor 94
Pravastatin 72	Sciatica 81	Titradose 9
Prazosin 19, 130	Seborrheic Dermatitis 92	TMP/SMX 54
Precose 78	Secretory Diarrhea 55	Tobramycin 34, 37, 44, 131
Prednisone 25, 90	Sectal 9	Tofranil 136
asthma 24	Seizure 63	Tolectin 83
Premarin 111, 115-117	Seizures 63	Tolmetin 83
Premenstrual Syndrome 108	Sensory Evoked Potentials 85	Toprol XL 18
Prempro 115, 117	Septa 25, 28, 30, 36, 132	Toradol 58, 83
Presyncope 61	Serax 141	Tornale 24
Prevacid 46, 48	Serevent 24	Torsemide 13
Prilosec 46, 48	Sertraline 137	Toxoplasmosis Prophylaxis 32
Primacor 14	Serzone 137	Transderm-Nitro 8
Primaxin 28, 37	Sestamibi 8	Transurethral Resection of the Prostate 131
Prinivil 13, 18	Sexually Transmitted Diseases 123	Tranxene 140
Probenecid 122	Shigella 54	Trazodone 137
Procardia XL 10	Shigelloides 54	Trental 76
Prochlorperazine 62	Simulated Defecation 51	Tretinoin 87
Progestasert 106	Simvastatin 72	Triamcinolone 23-25, 30, 90
Progesterone challenge 110	Sinequan 136, 141	Triamterene-hydrochlorothiazide 17
Propranolol 9, 18, 60	Single photon emission computer tomography 8	Triamterene/hydrochlorothiazide 17
Propranolol LA 60	Sinusitis 29	Triazolam 142
Propulsid 46, 51	Sitzmarks Test 50	Trichloroacetic acid 127
Proscar 130	Skin infections 96	Trichomonas Vaginitis 126
ProSom 143	Skin warts 90	Trimethoprim/SMX 25, 28, 30, 36, 37, 132
Prostate Specific Antigen 129	Smoking cessation 25	Triphasil 104
Prostatism 129	Solu-Medrol 24, 25	Tritec 48
Prostatitis 131	Soma 84	Trogitazone 80
Prostatodynia 131, 132	Sorbitol 51	
ProStep 26	Spectazole 93, 95	
Protease Inhibitors 32	Spironolactone 108	
Protriptyline 136	Sporanox 93-95, 126	
Provera 107, 111, 115-117	Squamous Intraepithelial Lesion 102	

Tuberculosis 41
 Tums 117, 118
 Type I diabetes 72
 Type II diabetes 76
 U-90 32
 Ulcer 47
 Ultravate 90
 Unasyn 28
 Uniphyl 24
 Univasc 18
 Urea Breath Test 47
 Urinary Tract Atrophy 114
 Urinary tract infection 35
 Uterine Bleeding 118
 Vaginal infections 124
 Vagotomy 48
 Valacyclovir 38, 40
 Valisone 98
 Valium 62, 140
 Valproic acid 60, 65
 Valtrex 38, 40
 Vantin 28, 30
 Vascor 10
 Vaseretic 19
 Vasocon-A23
 Vasotec 13, 18
 Vasovagal Reflex 61
 Venlafaxine 137
 Ventolin 24, 25
 Verapamil SR 10, 19
 Verruca Vulgaris 89, 90
 Verrusol 91
 Vertigo 60, 61
 Vestibular Neuronitis 61, 62
 Vibra-Tabs 28
 Vibramycin 25, 28, 122, 123,
 131, 132
 Vibrio parahaemolyticus 52
 Videx 32
 Viramune 32
 Viranol 91
 Visine 23
 Visken 18
 Vitamin D 116, 118
 Vivactil 136
 Warts 90, 127
 Wellbutrin 137
 Wigraine 58
 Xanax 109, 140
 Zafirlukast 24
 Zalcitabine 32
 Zantac 45, 47, 48
 Zaronin 65
 Zebeta 9
 Zerit 32
 Zestril 13, 18
 Zidovudine 32
 Zileuton 24
 Zinacef 28
 Zithromax 25, 28, 30, 97, 124
 Zocor 72
 Zolof 137
 Zolpidem 142, 143
 Zostrix 40, 76
 Zosyn 28, 36
 Zovirax 38, 40
 Zyflo 24
 Zyrtec 22

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